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THE FIFTEENTH OBSERVANCE OF NATIONAL PHARMACY WEEK, OCTOBER 22 TO 28, 1939.

The time is rapidly approaching for this Observance. During the past fourteen years great progress has been made in correcting the false impression held by the public about our profession. The 1939 National Pharmacy Week Committee solicits the coöperation of every pharmacist in America in making this year's observance the most successful in history. To most of us, it is not strange that although few professions require more training, more skill, more knowledge or more care in execution than Pharmacy, as a whole the public does not hold our profession in high esteem. Most pharmacists know that this present condition has been brought about by the desire of the pharmacist to have drugs and medicines readily available in every community and locality and that such service could not be maintained by the sale of drugs alone.

National Pharmacy Week has done much to raise the standards of Pharmacy and impress the importance of Pharmacy on the minds of the people, but, there is much more to be done. Our success will be in direct proportion to the coöperation received from our fellow pharmacists. This year's Committee has arranged a very extensive program.

Let us all do our part. It would be very gratifying to see a professional window in every drug store in the United States. And this could be accomplished if every pharmacist was determined to do his part. The National Committee has tried to make the task of installing these professional windows very easy by preparing three Model Windows. (See opposite page.) Each window can be installed in thirty minutes and is relatively inexpensive.

This year the publications of Rotary International, Lions International, Kiwanis International, Coöperative International and Cosmopolitan International will give wide publicity to National Pharmacy Week, and recommend to the local clubs that they invite a pharmacist to speak on Professional Pharmacy during the Week. If you are asked to speak at one of these meetings, please do not hesitate, and if desired the National Committee will mail you a fifteen minute suggested talk.

RECOMMENDATIONS.

The National committee recommends that each State Pharmacy Week committee divide its state into districts and through a chairman of each district solicit and encourage every pharmacist to install a professional window during Pharmacy Week.

The National Committee also recommends that each state committee contact its local radio stations and arrange for one or more fifteen minute talks on professional pharmacy to be given by prominent local pharmacists during this week.

The National Committee believes that the radio program called, "The Man on the Street" can also be effectively used and recommends that the local, state and city Pharmacy Week Committees arrange with their local radio stations for the Master of Ceremonies of these programs to interview a pharmacist at least once during National Pharmacy Week. The National Committee has prepared a set of questions and answers suitable for such an interview and will be glad to furnish such to anyone upon request.

The National Committee is encouraging hospital pharmacists to prepare scientific displays in the lobby of their hospitals. Any one of the three Model Pharmacy Week Windows will be very suitable for such a display.

It is the desire of the National Committee that the local, state and city committees arrange with their governors and mayors for a declaration of National Pharmacy Week and also for articles in the local newspapers and other publications.

The Committee also solicits the coöperation of the Colleges of Pharmacy and Pharmaceutical Associations in arranging suitable Pharmacy Week displays.

PHARMACY WEEK NATIONAL WINDOW DISPLAY PRIZE AND HONORABLE MENTION CERTIFICATES.

As in former years, the Robert J. Ruth Memorial Trophy consisting of a silver loving cup donated by the Federal Wholesale Druggists Association, will become the permanent possession of the winner in the National Pharmacy Week Window Display Contest. In addition to this prize, there will be awarded jointly by the AMERICAN PHARMACEUTICAL ASSOCIATION and the National Association of Retail Druggists to the ten next best window displays, Honorable Mention Certificates which when framed will prove to be interesting certificates for the interior of the store as well as for professional window displays. Entries in the National Contest are limited to the photographs of the winning displays in the state contests.

RULES OF THE NATIONAL CONTEST.

(1) Photographs of professional window displays must be submitted to the Secretary of the State Pharmaceutical Association on or before November 15, 1939, in order that the winner may be judged and entered in the National Contest.

(2) Photographs as submitted in former years will be ineligible.

(3) Photographs should be accompanied with a brief descriptive text together with letter of transmittal.

(4) Photographs should be 8 x 10 inches in size, or some other suitable size, so that the judges will be enabled to study details of the display.

Numerous other prizes in the form of silver loving cups, mortars and pestles, etc., will be awarded by state, county and local pharmaceutical organizations. The

Secretaries of the State Associations can furnish information about such contests and the awards.

PHARMACY WEEK AWARDS FOR ASSOCIATIONS AND COLLEGES.

The AMERICAN PHARMACEUTICAL ASSOCIATION will present to the state, county or local pharmaceutical organization a Pharmacy Week award for the best professional window display as prepared and featured by the organization. The award last year was won by the Philadelphia Association of Retail Druggists. Another award will be presented to the College or School of Pharmacy which prepares and features the best professional window display. The award last year was won by the Temple University School of Pharmacy. Photographs should reach the National Pharmacy Week Committee before December 15th.

NATIONAL PHARMACY WEEK RADIO BROADCASTS.

Arrangements have been made for addresses by representatives of the AMERICAN PHARMACEUTICAL ASSOCIATION over the national broadcasting networks. Watch for announcements of the date and time of these broadcasts.

PHARMACY WEEK ARTICLES.

The human interest Pharmacy Week articles have proven to be a very helpful feature of Pharmacy Week observance. Thousands of copies were distributed last year and the series has been revised with the hope that a larger number will be used this year. An announcement of the titles, etc., of these articles, will be made later.—JOHN E. O'BRIEN, *Chairman*.

FOR DISTINGUISHED SERVICE.

Under this appropriate heading, *The State Journal* of Frankfort, Ky., devoted a column in its issue of June 23, 1939, to paying a splendid tribute to John W. Gayle who had, just a few days before, retired as secretary of the Kentucky Pharmaceutical Association after having served in that office continuously since 1889, or half a century. It was stated that Mr. Gayle can look back on fifty years fruitful with accomplishment. He was given credit for the enactment of the pharmacy law and the narcotic law of the state and for many services to its citizens as well as the pharmacists.

"Honors have been heaped upon this Frankfort man, who, despite his eighty years, is active in his private business and keenly alert to the problems and progress of Pharmacy. For forty-one years he served as secretary of the Kentucky Board of Pharmacy and was associated with the formation of the National Association Boards of Pharmacy. He was elected their treasurer in 1919, a post he has held for the past twenty years. In 1891 he became a member of the AMERICAN PHARMACEUTICAL ASSOCIATION and by virtue of continued membership is now a life member. He was the ASSOCIATION'S vice-president in 1914."

Tribute was also paid to Mr. Gayle in the July issue of the *Kentucky Pharmacist* from which the following is quoted:

"We don't know of any way to thank J. W. Gayle, other than to say our simple, 'Thank you, sir.'"

The Association paid its simple and humble tribute to "The Skipper" when he was elected Secretary Emeritus of the Association at the Friday morning session. On Thursday night, at the banquet, he was presented with a gold plaque, bearing the following inscription: "Presented to J. W. Gayle, by the Kentucky Pharmaceutical Association as a Token of Esteem and in Appreciation of his Fifty Years of Faithful Service as Secretary, 1889–1939;" plain words, but sincere.

It is evident that this record of service will stand for some time as a fitting memorial to a distinguished gentleman and a faithful member of our profession.

EDITORIAL

E. G. EBERLE, EDITOR EMERITUS. 2215 Constitution Ave., WASHINGTON, D. C.

THE PRACTICE OF MEDICINE HELD TO BE A PROFESSION AND NOT A TRADE.

It will be recalled that some months ago the American Medical Association, the District of Columbia Medical Society and others were indicted in the Federal Court of the District of Columbia. The indictment charged a conspiracy to restrain trade in the District of Columbia in violation of Section 3 of the Sherman Anti-Trust Act. It was charged that the defendants were conspiring to prevent the Group Health Association, Inc. from arranging for the provision of medical care and hospitalization to its members, largely government employees, on a "risk-sharing prepayment basis." The defendants filed demurrers making basic objections to the indictment, the most important of which were that the acts complained of were not restraints of trade and that the practice of Medicine was not a trade within the meaning of the law.

On July 26, 1936, Justice James M. Proctor of the United States District Court for the District of Columbia, sustained the demurrers to the indictment in an opinion which deals with these two questions exhaustively and which deserves careful study by all who are interested in preserving the accepted status of the professions. Justice Proctor held that the practice of Medicine is a profession and that the learned professions are clearly excepted from the provisions of the law. Justice Proctor also held that "if the livelihood of group practitioners has been injured by the wrongful acts of the defendants, they too have redress in a civil court."

The Anti-Trust Division of the Department of Justice promptly gave notice that a reversal of the decision will be sought and later a notice of appeal to the United States Court of Appeals was filed in which seven reasons were stated why the decision is erroneous. It is also indicated that a new indictment may be sought with the object of taking the case directly to the U. S. Supreme Court. A final decision may not be rendered for some time.

This case has taken on unusual importance because of the basic questions involved with respect to the adequacy of medical care and to its cost and the press comment on Justice Proctor's opinion was wide spread and outspoken. There was general agreement with the clear distinction between a profession and a trade in the opinion, and that the indictment was not sound. There was sharp criticism of the Government's attitude and procedure. It was generally recognized, however that even though the opinion of Justice Proctor is upheld, this will not settle the broad underlying problem of improving and extending medical services for the people. One paper referred to the present situation as being unsatisfactory and continued, "But this condition will be improved. It will be a slow and long process, toward the ideal medical provisions for the entire nation. One thing, however, is certain. It will only be reached with the coöperation of the healing professions. Without them, any such effort is foredoomed to failure."

It would seem to be the part of wisdom as well as a duty for the health professions to coöperate actively and earnestly in working out more adequate and more reasonable provisions for medical services, at the same time resisting any effort to impose on them any form of control which will interfere with the effective discharge of their age-old duties and responsibilities to the people.—E. F. K.

SECTIONS

BOARD OF REVIEW OF PAPERS (SCIENTIFIC SECTION).—*Chairman*, F. E. Bibbins; H. M. Burlage, W. G. Crockett, E. V. Lynn, C. O. Lee, L. W. Rising, L. W. Rowe, Heber W. Youngken, Ralph E. Terry, Carl J. Klemme.

INSECT INFESTATION OF DRUGS.*,[1]

BY BERNARD L. BLUMBERG.[2]

INTRODUCTION.

Records of insect infestation in drugs during the last sixty years have been numerous. Unfortunately, however, the majority of these records remain scattered throughout the literature, and represent observations on the material at hand without any attempt to systematize, corroborate or extend the data previously accumulated. Some workers such as Sayre (4), Tschirch (5) and Stuhr (1) have made compilations dealing with many of the drugs liable to insect attack, a simplified (for pharmaceutical purposes) entomological discussion of the pests, and methods of control. Many of the textbooks on Pharmacognosy have treated this subject similarly, but all have, for the most part, omitted the purely pharmacognostical aspects of the topic. Information as to the chemical and botanical alterations produced by infestation, the identification of insect fragments in drugs, etc., is disconcertingly meager.

The importance of the subject is adequately recognized in the General Notices of the U. S. P. XI (6) wherein it is stated that vegetable drugs are to be as free as practicable from insects and other animal life, animal material or animal excreta. The same reference states that the following drugs are particularly liable to the attack of insects: aconite, belladonna root, cantharides, capsicum, caraway, cardamon, ergot, ginger, glycyrrhiza, linseed, myristica, rhubarb and sarsaparilla.

In the same section of the Pharmacopœia there are directions for the preservation of drugs against insect attack, but nowhere is there an analytical procedure for determining the presence of insects or their fragments in drugs, or a general paragraph describing the distinguishing features of a powdered insect infested drug. This statement also applies to the standard unofficial books often consulted by the pharmacognocist.

The purpose of this paper is to review the literature available on the pharmacognostical aspects of infestation, and to present experimental data on the rôle of *Tribolium* beetles as drug pests. It is realized that the present report does not follow through several of the problems which have arisen in connection with the project, but it is hoped that in the future, research will be done on some of the points mentioned; inclusion in pharmacognosy texts of the results accumulating therefrom should be very enlightening and of practical value.

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* Presented before the Scientific Section, A. PH. A., Minneapolis meeting, 1938.

[1] A condensation of Part I of a dissertation to be presented in partial fulfilment of the requirements for the degree of Doctor of Pharmacy in Columbia University, College of Pharmacy. The work is under the direction of Dean C. W. Ballard, Professor of Materia Medica.

[2] From the Pharmacognosy Laboratory, Columbia University, College of Pharmacy.

INFESTING INSECTS AND DRUGS ATTACKED.

From a bibliographical research it has been possible to compile a list of forty-seven infesting insects and eighty-two drugs which they attack. Seven miscellaneous items of pharmaceutical interest which are subject to attack, and eleven drugs resistant to infestation, have likewise been compiled. Owing to limitations of space, these cannot be included here. Interested readers may communicate with us for further details.

CONSTITUENTS AND STRUCTURES REMOVED FROM DRUGS BY INSECTS.

Stuhr in a recent investigation (1) says that in general those drugs rich in starch, inulin and sugars are most liable to insect attack. His opinion, especially as concerns starch, seems to be a well established fact, although one finds few experiments to substantiate it. On the other hand, an opinion to the contrary, on the basis of experimentation, has been expressed by Greenish and Braithwaite (2). These two workers cite the following results:

Examination of the powder collected from the bottom of a jar containing ginger infested with *Sitodrepa panicea* "shows that the powder consists almost entirely of small pellets of the excrement of the larvæ. . . . We were surprised to find that it consisted almost wholly of starch, some few grains of which showed evidence of partial digestion. While, therefore, the larva undoubtedly ingests considerable quantities of starch, only a small proportion of this would appear to be digested. Similarly, larvæ living on dandelion root excrete abundant fragments of tissue in which inulin is still to be found. In the case of coriander fruit, the endosperm upon which the larva feeds is free from starch, but contains fixed oil and abundant aleurone grains, in each of which a rosette of calcium oxalate is to be seen embedded in ground substance; the quantity of excrement is small and consists of portions of various tissues together with some oil globules and numerous calcium oxalate rosettes now devoid of nitrogenous substances such as the remains of protoplasm, etc."

The presence of the lactiferous vessels of dandelion root in the excrement lead the same workers to doubt the correctness of the statement that the larvæ avoid those portions of the drug containing the active constituents. They further state that in aconite and belladonna roots, and doubtless others in which the alkaloids are stored in the parenchymatous tissue within the cork and in that near the bast ring, it is quite probable that the tissues are ingested by the larva when boring into the root.

Greenish and Braithwaite's conclusions are subject to some criticism. Inasmuch as ginger contains about 45% starch, it is possible that large quantities of the starch could be digested by the beetles and that it would still preponderate in the excreta. Carefully controlled quantitative experiments would seem necessary to justify the conclusions that a considerable amount of the carbohydrates of ginger are not utilized by insects. The same comment may apply to taraxacum which contains about 25% inulin. In the case of coriander it is quite probable that the beetle utilized the nitrogenized aleurone grains and some of the oily or fatty substances.

Notwithstanding these experiments, the results of our research appear to indicate that fair amounts of carbohydrates (especially starch) are consumed by the insects. However, it must not be assumed that carbohydrates alone are an adequate diet; they probably are supplemented by either proteins and/or fats if the beetle is to enjoy a normal life cycle.

Maier and Ballard (7) undertook a chemical and microscopical examination of wormy rhubarb to determine its anthraquinone content. The investigation was initiated after a discussion with a dealer who said that wormy belladonna roots and aconite contain relatively more alkaloid than the sound drug, because the starch was consumed by the insect. They observed that the starch content decreased and the fibrovascular tissues, parenchyma and calcium oxalate increased as the infestation progressed. The anthraquinone content increased relatively to a certain limit beyond which there was a diminishing, probably due to decomposition. The laxative properties were never entirely lost even in very old and wormy specimens.

The diminution of starch concomitant with infestation was confirmed by Denston (3) who examined licorice stolons infested by a species of *Lyctus*. Borings were present mainly in the xylem and pith. Powders from the borings were examined microscopically and showed the

presence of circular or oval masses about 80μ in diameter and smaller fragments not exceeding 15μ. On disintegrating the masses with chloral hydrate, fragments of cellulosic parenchyma, lignified fibers and thickenings of the vessel walls were evident; the latter greatly predominated. Fiber fragments were relatively few and there was little calcium oxalate. The proportion of starch in the powder was considerably less than in normal licorice. The most characteristic feature was the fragments of reticulate and pitted walls of vessels.

Denston also reports the microscopical examination of a coarse, somewhat granular, dark green powder formed in stramonium by *Ptinus tectus*. The material was almost entirely in narrow rectangular pieces 300–600μ long and 50–120μ wide. Pieces had been cut from the leaves and flowers in irregular directions, but the midribs and petioles did not appear to have been attacked. Thus the powder showed all the elements of stramonium leaf and flower except the larger vessels such as are present in the midrib and petiole.

PHYSICAL CHANGES ASSOCIATED WITH INFESTATION.

The physical changes identifiable in whole and powdered drugs include web formation, borings and tunnels and gnawings. Such alterations usually result in the formation of powder.

ANALYTICAL PROCEDURE FOR IDENTIFICATION OF INSECT FRAGMENTS IN DRUGS.

The only analytical procedure that this author has found in the literature for the identification of insect fragments in drugs is that of Greenish and Braithwaite (2). They prepared powders from infested crude drug stock and employed the following method:

Defat 5 Gm. of powder with ether in a Soxhlet; dry the defatted powder and boil with 100 cc. of 5% HCl for five minutes in a tared flask; add about 150 cc. water, allow the powder to settle and wash once by decantation. For every 35 Gm. of water and powder in the flask, add 6 cc. conc. H_2SO_4, cool, and then add in small portions and cooling again if there is any considerable rise in temperature, 10 cc. of a 1 in 1 aqueous solution of chromic acid. Allow the mixture to stand with occasional agitation for 36 hours or longer. Separate the solid particles by centrifugation, wash then with water, alcohol and ether successively, dry, remove from tube and mount in xylol balsam.

Variations in the method may be necessary with different powders; thus, if the drug contains little material that is ether soluble the treatment with this solvent may be omitted, and similarly that with HCl. The residue in the centrifuge tube may be examined at once under the microscope if a permanent record is not desired. Eighteen hours often suffices, but a better result is obtained by allowing the oxidizing mixture to act 36–48 hours after which time the residue will consist of little else than sand and beetles. The particles of beetles are readily detected by their conspicuous color, and most of them will exhibit either hairs or scars of hairs.

This method was tested quantitatively by mixing 5 Gm. of powdered rhubarb with 0.00001 Gm. of *Sitodrepa* (contained in a milk sugar trituration). Since the authors had previously studied the covering parts of the *Sitodrepa panicea* body microscopically, they could accurately identify the several fragments of beetle contained in the residue. It would appear that one mature beetle in every Gm. of powder is indicative of a highly infested condition.

The authors also include a table of results for ten different powdered drugs and spices tested by this method.

The principal shortcoming of this method is that it does not attempt to detect insect eggs or the softer parts of the immature forms of the insect. Detection of the eggs may be of considerable practical importance, when an insect infested drug has been so reconditioned that all of the larger forms are removed.

Tribolium INFESTATION IN DRUGS.

Since *Tribolium* beetles have not heretofore received much consideration as drug pests, one may wonder why we have experimented with these beetles. Our investigation seems justified in view of the following: (1) The losses caused by insects injurious to stored grain and milled products in the United States represent about $250,000,000 annually. According to one report (14) 84.65% of all species of insects removed from mill streams of flour mills during 1934–1935 were *Tribolium*. (2) We have quite frequently found dead *Tribolium* beetles in our own drug

stock, although the only drug with which live insects seem to have been definitely associated was linseed. (3) There are records of the occurrence and depredations of *Tribolium* from practically every civilized country in the world. Its ubiquity alone may make it a potential drug infester. (4) According to previous reports (8, 9) *Tribolium confusum* has been bred in orris root and in cayenne pepper with some difficulty; it feeds on nutmeg, mustard, ginger and cinnamon, and may utilize elm bark as a source of food.

Probably the most serious insect drug pest is *Sitodrepa panicea* (the drug store beetle); its omnipresence and destructiveness in drug fields closely parallels that of *Tribolium* (the flour beetle) in grains and stored products.

EXPERIMENTAL DATA.

Procedure.—The same method of handling, counting, etc., was employed throughout our experiments, the only variable factor being the type of receptacle in which the drugs were contained. In earlier tests we used 1 by 4 inch vials for the powders and four-ounce wide-mouthed jars for the whole drugs; each container was loosely stoppered with cotton. Because of the difficulty in finding and counting the beetles, we next tried 100 cc. unstoppered beakers for holding the powders; these permitted a more facile handling of the insects than the vials, but still did not seem completely satisfactory. We finally resorted to using 10 cm. petri dishes, and found them very suitable. In many cases the ten beetles used in each experiment could be observed in the petri dishes without disturbing the substrate. No specific experiments were run to determine whether the difference in air and moisture exchange in a closed petri dish as compared with that in a cotton-stoppered vial or an open beaker would affect the longevity of the beetles. However, we consider this factor negligible inasmuch as we have kept *Tribolium* adults alive for more than eight months in closed petri dishes.

The beetles used in the experiments were cultured in either wheat or barley flour kept in a dark place at room temperature (21–23° C.). Whenever insects were required for experimentation, teaspoonfuls of the infested flour were transferred to a 4XX silk bolting cloth, most of the flour was removed by very gentle sifting, and then the beetles were dislodged into a petri dish by means of a small camel's hair brush. It was usually necessary to transfer the insects from this dish to a second in order to remove all the adherent flour and extraneous material. There was no attempt to select insects of a definite age or sex; those used were apparently healthy, normal, active adults.

The drugs employed were of U. S. P. quality and showed no signs of insect infestation as revealed by a thorough macroscopic examination, although beetles other than *Tribolium* developed in some of the orris and ginger at a later date (see Table V). Approximately ten Gm. of all drugs, whole and powdered, were used.

For each trial ten beetles were placed in a petri dish with ten Gm. of the drug. As indicated in the tables of results, some dishes were kept at room temperature (21–23° C.), and others were placed in a thermostatically controlled incubator at 26–28° C. Mortality examinations were conducted by making an actual count of the number alive and dead, taking care not to disturb the individuals unnecessarily. (Chapman (10) has found that frequent handling increases the death rate of the beetles.) The mortality figures listed do not represent the maximum time that a certain number of beetles lived, but rather the number of beetles dead at the time observed.

RESULTS.

TABLE I.—10 GM. MATERIAL—10 BEETLES—DARK PLACE—IN UNSTOPPERED BEAKERS—POWDERED DRUGS AT 26–28° C.

Substance.	Mortality in Days. 4.	6.	11.	22.	33.	60.
R. rhaponticum—SBP	3	8	10	..	..	..
R. rhaponticum—CUCP	1	4	10	..	..	..
Krameria	2	10	..	..	..	..
Geranium	10	..	..	..	..	..
R. officinale—SBP No. 3344	3	8	10	..	..	..
R. officinale—CUCP	3	4	10	..	..	..
R. officinale—No. 129	6	9	10	..	..	..

TABLE I.—10 GM. MATERIAL—10 BEETLES—DARK PLACE—IN UNSTOPPERED BEAKERS—POWDERED DRUGS AT 26–28° C. (*Continued from page 486.*)

Substance.	Mortality in Days. 4.	6.	11.	22.	33.	60.
R. officinale—CWB No. 10307	4	7	9	10	..	..
R. officinale—CWB No. 10307	..	..	8	10	..	..
R. officinale—SBP No. 51972	3	8	10	..	..	..
Rubus	1	5	10	..	..	..
Tannic acid 10%—corn starch	..	..	..	9	10	..
Tannic acid 15%—corn starch	..	..	..	9	10	..
Tannic acid 20%—corn starch	..	3	6	10	..	..
Aloin 1.5%—corn starch	0	0	0	1	1	1
Aloin 3.0%—corn starch	0	0	0	3	3	3
Aloin 4.5%—corn starch	0	0	1	3	3	9
Calcium oxalate 3%—corn starch	0	1	2	6	7	8
Calcium oxalate 5%—corn starch	0	0	0	3	6	9
Calcium oxalate 7%—corn starch	0	0	1	2	5	8
Tannic acid 15%, calcium oxalate 5%, corn starch 80%	0	1	6	10	..	..
Tannic acid 15%, calcium oxalate 7%, corn starch 75%, aloin 3%	0	4	10	..	..	..
Corn starch (control)	..	..	..	2	2	3

TABLE II.—SAME CONDITIONS AS TABLE I, BUT AT 21–23° C.

Substance.	Mortality in Days. 4.	6.	11.	22.	33.
R. rhaponticum	..	3	7	10	..
R. officinale—SBP No. 3344	..	1	5	10	..
R. officinale—SBP No. 51972	..	1	5	10	..
Krameria	..	..	2	8	10
Geranium	2	..	10	..	..
Rubus	..	..	9	10	..

TABLE III—SAME CONDITIONS AS TABLE II.

Substance.	Mortality in Days. 7.	15.	35.	37.	45.	59.
R. officinale—No. 129	0	0	..	10	..	..
R. officinale—No. 129	..	..	10	..	..	..
Aloin 1.5%—corn starch	0	0	..	..	3	3
Aloin 3.0%—corn starch	0	0	..	..	2	2
Aloin 4.5%—corn starch	0	0	..	..	2	2
Tannic acid 5.0%—corn starch	0	0	..	..	2	2
Tannic acid 10.0%—corn starch	0	0	..	..	2	*
Tannic acid 15.0%—corn starch	0	0	..	..	8	*
Corn starch (control)	0	0	..	..	1	2

* Dishes accidentally destroyed.

TABLE IV.—10 GM. MATERIAL—10 BEETLES—IN COTTON-STOPPERED JARS AND VIALS—26–28° C.

Substance.	Whole Drugs. Mortality in Days. 14.	21.	26.	31.	45.	53.	67.	83.	Powdered Drugs. Mortality in Days. 12.	21.	33.	38.	52.	60.	74.	90.
Aconite	10	..	..	..	..	..	..	..	10	..	..	..	..	..	..	..
Althea Root	5	..	..	10	..	..	..	..	6	8	8	9	9	..	..	9
Belladonna Root	5	..	9	10	..	..	..	..	10	..	..	..	..	..	..	..
Cantharides	..	4	10	..	..	..	..	..	9	..	..	10	..	..	..	..
Capsicum	..	10	..	..	..	..	..	..	9	..	..	10	..	..	..	..
Caraway	..	10	..	..	..	..	..	..	6	8	10	..	..	..	..	..

TABLE IV.—10 GM. MATERIAL—10 BEETLES—IN COTTON-STOPPERED JARS AND VIALS—26–28° C.

(*Continued from page 487.*)

Substance.	Whole Drugs. Mortality in Days. 14.	21.	26.	31.	45.	53.	67.	83.	Powdered Drugs. Mortality in Days. 12.	21.	33.	38.	52.	60.	74.	90.
Cardamon (whole)	..	10	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Cardamon (decorticated)	..	10	..	..	..	..	..	..	1	3	4	5	6	7	7	9
Ergot	..	6	6*	..	6*	6[2]	[1]	[1]	3	4	4	4*	4*	4	[1]	[1]
Ginger (Jamaica)	6	7	9	..	9	10	..	..	..	..	..	..	..	..	..	..
Linseed	..	6	8	..	9*	..	..	..	..	..	..	..	..	..	..	..
Myristica (limed)	10	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Myristica (washed)	..	9	10	..	..	..	..	..	..	..	..	..	..	..	..	..
Rhubarb	10	..	..	..	..	..	..	..	10	..	..	..	..	..	..	..
Sarsaparilla (Mex.)	10	..	..	..	..	..	..	..	10	..	..	..	..	..	..	..
Sarsaparilla (Hond.)	10	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Glycyrrhiza (Span.)	10	..	..	..	..	..	..	..	10	..	..	..	..	..	..	..
Glycyrrhiza (Russ., whole)	10	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Glycyrrhiza (Russ., cut)	..	8	10	..	..	..	..	..	10	..	..	..	..	..	..	..
Althea Leaf	10	..	..	..	..	..	..	..	10	..	..	..	..	..	..	..
Corn starch (control)	..	..	..	..	..	..	..	..	1	1	..	..	2	2	4	4

* Live larvæ present

[1] New adult present

[2] One pupa present

TABLE V.—10 GM. MATERIAL—10 BEETLES—DARK PLACE—IN PETRI DISHES—26–28° C.

Substance.	Whole Drugs. Mortality in Days. 11.	22.	36.	52.	Powdered Drugs. Mortality in Days. 11.	22.	36.	52.
Pillsbury 4X Flour (control)	..	..	..	..	..	1[1]	1	1
Pillsbury 4X Flour (control)	..	..	..	..	..	1[1]	1	2
Corn starch (control)	..	..	..	..	..	0	1	3
Corn starch (control)	..	..	..	..	..	1	2	3
Orris Root	5[3]	6	8[3]	8[3]	3	8	10	..
Orris Root	1	6	8[4]	10	4	7	9	9
Ginger (Jamaica)	7	7	9	10	4	7	10	..
Ginger (Jamaica)	3	6	7	7[5]	7	10	..	..
Capsicum	5	10	..	..	10	..	..	..
Capsicum	8	10	..	..	10	..	..	..
Ulmus	1	10	..	..	9	10	..	..
Ulmus	6	10	..	..	10	..	..	..
Myristica	..	..	..	..	6	10	..	..
Myristica	..	..	..	..	6	10	..	..
Mustard (black)	6	10	..	..	10	..	..	..
Mustard (black)	6	10	..	..	8	10	..	..
Cinnamon	10	..	..	..	10	..	..	..
Cinnamon	9	10	..	..	9	10	..	..
Linseed	1	2[2]	3[2]	3[1]	2	4[2]	6	6[1]
Linseed	1	3	5	5	1	1[2]	2	*

* New adult present.

[1] Heavily infested with larvæ.

[2] Live larvæ present.

[3] One live larva present. Matured at 36 days; adult not *Tribolium*.

[4] One live beetle (not *Tribolium*) present.

[5] Two live beetles (not *Tribolium*) present.

DISCUSSION OF RESULTS AND CONCLUSIONS.

Before proceeding with a general discussion of the results, it should be explained that our inference as to whether or not a drug was favorable to *Tribolium* nutrition,

was based on two facts—the results in the control, and a statement by Good (9) who has observed that the average life of the adult beetles is more than one year, and that adults may resist starvation from fourteen to fifty-one days.

The experiments in Tables I, II and III were undertaken in an attempt to determine what constituents of rhubarb were toxic to *Tribolium* Before this investigation was initiated it was expected that rhubarb would be susceptible to attack by *Tribolium*. After testing several different samples and finding them toxic, we made chemical mixtures using the proportions of the more important substances present in rhubarb as a basis. From the results in these tables, it may be inferred that tannic acid either in artificially or naturally occurring mixtures is unfavorable to *Tribolium;* its toxicity increases directly as the temperature. Aloin is practically innocuous at either 21–23° C. or 26–28° C., but seems to increase the toxicity of tannic acid and calcium oxalate in admixture with the two. Calcium oxalate seems to have a decidedly detrimental effect on *Tribolium*.

R. rhaponticum gives almost identical mortality results with *R. officinale*. Probably the toxicity of neither is influenced by alœemodin, emodin, rhein or rhaponticin, since the latter only is present in *R. rhaponticum* while the other three are found in *R. officinale* (11).

The tannic acid content of *R. officinale*, *R. rhaponticum*, geranium, krameria and rubus varies from 8–28%. All of these drugs are resistant to attack by *Tribolium*, and with the exception of the first two, all are resistant to insect infestation generally. While tannic acid may be a contributory factor, present experiments are insufficient to permit definite conclusions, and previous literature would seem to negate this idea. For example, Williams (12) states that Felt defines galls as "vegetable excrescences resulting from insect activity and usually sheltering immature states of the producers." He also notes that beetles feeding on plants frequently produce galls which they eat. Since galls generally have a high tannic acid content (13), it would seem unlikely that this substance is unfavorable to them.

Future breeding experiments should employ the marc of the drug as a diluent for an artificial drug mixture, instead of starch; while adult *Tribolium* beetles feed upon and enjoy a good span of life in corn starch, this writer has never found that they lay eggs or multiply in it in the time noted.

Table IV represents experiments on the drugs, in crude and powdered form, recorded in the general notices of the U. S. P. XI as being liable to insect attack. With the exception of ergot and linseed (see Tables IV and V), none of these drugs is subject to attack by *Tribolium*. Crude ginger and powdered althea root may be utilized (because of their starch?) for relatively long periods, but the beetles will not pass through a complete life cycle on either of these drugs.

The constituents of this group of drugs are so varied chemically that it is impossible at this time to theorize on their relation to drug susceptibility or resistance.

Table V was conducted for the purpose of verifying previous observations. (See section on *Tribolium* Infestation in Drugs.) Contrary to such observations it was found that *Tribolium* will not live in whole or powdered capsicum, elm bark, myristica, mustard and cinnamon. Orris root, whole and powdered, seems to sustain life for a short time; linseed, whole and ground, permits feeding and breeding. Powdered ginger killed all the beetles promptly, but the results on whole ginger

were somewhat vitiated by the presence of other insects (see Table V). Whereas our experiments would seem to indicate that the beetles starve to death on elm bark, Good (9) found that *Tribolium* could utilize this substance as an auxiliary food.

Perhaps the failure to breed *Tribolium* on capsicum was due to the fact that only ten beetles were employed in a single test. However, the same results obtained in four trials. Good (9) has bred this beetle in capsicum with some difficulty.

Of all the drugs included in the experiments, ergot and linseed were the only sufficiently favorable substrates for reproduction of the beetles.

SUMMARY.

1. An extensive list of insects attacking drugs and the specific drugs which they attack has been compiled from various sources.

2. The literature on the physical changes produced in drugs during infestation, and the chemical constituents and structures removed from drugs by insects, is presented. In general it would seem that carbohydrate containing drugs are quite susceptible to insect attack, but if other beetles, *e. g.*, *Sitodrepa panicea* may be judged by *Tribolium*, carbohydrates are not the only substances required. Protein and/or fats are also necessary.

3. *Tribolium* is not a serious drug pest; of the thirteen drugs listed in U. S. P. XI as being especially liable to insect attack, only ergot and linseed permitted this beetle to reproduce. Orris, ginger, althea root and decorticated cardamom sustained life for varying lengths of time.

4. Contrary to previous reports *Tribolium* could not be cultured in capsicum, nutmeg, cinnamon or mustard, and does not appear to utilize elm bark as an auxiliary food.

5. Tannic acid and calcium oxalate individually are unfavorable to *Tribolium*, while aloin has little effect.

6. It is recommended that further work be done on the pharmacognostical aspects of insect infested drugs with a view to furnishing more complete information on the chemical and botanical alterations produced in such drugs. This may ultimately influence official descriptions and standards. It is also suggested that an analytical method for the identification of insect fragments and eggs be perfected and included in standard pharmacognosy books. One such method previously devised is reviewed here.

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CHLOROBUTANOL.*

BY ARTHUR GEORGE FISHBURN AND HERBERT BEN WATSON.

Chlorobutanol (Chlorbutol, Chloretone, Acetone-chloroform) is described in the United States Pharmacopœia (XIth Revision) as trichlortertiarybutyl alcohol either anhydrous or containing up to about half a mol of water and having m. p. not below 78°; the British Pharmacopœia (1932) also describes the water of crystallization as variable, while the French Pharmacopœia (1937) formulates the compound with $^1/_2H_2O$ and gives m. p. 75–78°. The presence of addition compounds in mixtures of acetone and chloroform has been indicated by freezing point and dielectric polarization data (1), but these are probably quite distinct from chlorobutanol and the molecules have been represented as linked through the hydrogen atom of the chloroform.

In the usual preparation of chlorobutanol (2), (3), rather more than half an equivalent of potassium hydroxide is added (during a period of 48 hours or more) to a mixture of approximately molar quantities of acetone and chloroform. After filtration from the precipitated potassium chloride, a low-boiling fraction containing acetone and chloroform is removed by distillation, and the remaining liquid (A) treated with water. Nowhere does a yield much exceeding 10% of the theoretical seem to have been recorded. The liquid A was first thought to be an isomeride (2); the discovery that the treatment with water was accompanied by a loss of 13% of its weight, and that a similar liquid was obtainable by distillation of solid chlorobutanol with a little acetone, however, led to the conclusion that it was a mixture of chlorobutanol with some acetone (3).

EXPERIMENTAL.

We have treated mixtures containing varying quantities of acetone and chloroform with different substances. In absence of a catalyst no reaction occurred (as found by earlier workers). Nor was any product obtained when the reagents were brought together in presence of a little sulfuric acid, piperidine (3% of wt. of reagents), calcium hydroxide or ammonia (10% by wt.), borax, sodium carbonate or bicarbonate (up to 40% by wt.); neither long standing nor refluxing led to reaction. Solid sodium hydroxide was almost as effective as potassium hydroxide, but concentrated aqueous solutions were not so good.

Equimolecular quantities of reagents in presence of 5% or 10% of potash gave only 10% of the theoretical yield; an excess of acetone gave a much higher conversion of the chloroform, as follows:

Per Cent KOH (Referred to Wt. of $Me_2CO+CHCl_3$).	Mols. Me_2CO Per Mol $CHCl_3$.	Per Cent Yield (Calcd. on $CHCl_3$).
5 (added as solid or sat. alcoholic solution)	2	12–13
5 (ditto)	5	24–26
10 (added as solid)	5	18

When the potash is added in the solid state, there is a *slow* precipitation of potassium chloride (per cent KCl in ppt. from 97.3 to 98.4, compare ref. 3); on addition of a saturated solution of potash in alcohol, however, the precipitation is immediate and the yield is not improved by standing. The rate of reaction in the former case is probably governed by the slow solution of the potash. The addition of solid potash leads, moreover, to the development of a distinct

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yellow color which is retained to some extent by the product, but alcoholic potash gives a perfectly white product.

The formation of potassium chloride is due to decomposition of chlorobutanol by the alkali. The products of this decomposition are potassium chloride, acetone and carbon monoxide (compare ref. 3) according to the equation $Me_2C(OH)CCl_3 + 3KOH = 3KCl + Me_2CO + CO + 2H_2O$.

The liquid product A boils over a range of 165–170°, and solidifies fairly rapidly on exposure to air. If a considerable excess of acetone is used, the tendency to solidify is less marked and the loss of weight on addition of water is greater. Thus, in a preparation from 10 mols acetone and 1 mol chloroform this loss was as great as 25% of the weight of the liquid; this liquid, moreover, contained only 41.7% Cl, indicating 73% of trichlortertiarybutyl alcohol. If acetone and solid chlorobutanol are placed in separate open vessels in the same desiccator, the chlorobutanol liquefies after a few hours but begins to solidify when the desiccator is opened.

In order to gain information regarding the substance which is removed by water from the liquid product A, we added 2:4-dinitrophenylhydrazine hydrochloride to the aqueous solution obtained after filtration of the solid chlorobutanol. This gave a red product which was purified (with but little loss) by three extractions with boiling alcohol. The residue, which was identical with the crystalline product from the third extract, had m. p. 200°, and was quite different from the 2:4-dinitrophenylhydrazone of acetone (yellow, m. p. 128°). This observation led us to prepare a specimen of diacetone alcohol (b. p. 166°, soluble in water) by the method described in *Organic Syntheses* (4), and this gave a 2:4-dinitrophenylhydrazone identical with the red product described above (m. p. 200°).

Solid chlorobutanol, crystallized from aqueous alcohol, melts at 77°. Its chlorine content is 57.1%, and it is therefore a hydrate with $^1/_2H_2O$ (Cl required, 57.1%). The crystals form two layers on melting; the upper aqueous layer distils first on further heating, and finally anhydrous chlorobutanol distils at 166°. Specimens of this compound after 72 hours in a vacuum desiccator in tubes sealed immediately after removal melted at 96.2° (Cl 60% as required). On exposure to air the m. p. fell to 77° after 25 mins., and thereafter remained constant.

SUMMARY AND CONCLUSIONS.

Our results show that the activation of the carbonyl bond which is necessary for the production of chlorobutanol from acetone is brought about only by a very strong base; weaker bases and acids are ineffective. The failure of calcium hydroxide to exert any influence may be due to its insolubility in the reaction mixture. The best results are obtained when an excess of acetone is employed. In view of the decomposition of the product by potash, the yields are never good, and a relatively small quantity of the catalyst is advantageous.

The liquid product obtained from acetone, chloroform and potassium hydroxide contains diacetone alcohol, with which, it may be presumed, chlorobutanol forms some type of constant boiling mixture. This substance is removed by water, and the product is a solid of the formula $Me_2C(OH)CCl_3.^1/_2H_2O$ (m. p. 77°) The anhydrous compound (m. p. 96.2°) is converted into this hydrate on standing in air for less than half an hour.

We recommend the following procedure for the preparation of chlorobutanol. One hundred grams acetone (5 mols) and 40 Gm. chloroform (1 mol) are mixed, and 7 Gm. potassium hydroxide (5%) dissolved in the minimum quantity of alcohol, are added. The addition occupies fifteen minutes; cooling is usually unnecessary. The precipitated potassium chloride is filtered off and washed with a little acetone. The filtrate is distilled on the water-bath and when no further liquid distils about 200 ml. of water are added. The chlorobutanol is filtered off as a white solid. Yield (calc. on $CHCl_3$), 25% theoretical. The acetone distilled off is used in a subsequent preparation.

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STUDIES ON THE GLUCOSIDES CONTAINED IN TAXUS BREVIFOLIA.

BY GEORGES MASSON.*

In a study made by I. Jones and E. V. Lynn (1), the authors report that they attempted the isolation and identification of the glucosides contained in *taxus brevifolia* and especially for taxicatine as found by Lefevre (2) in *taxus baccata*. They used the method of extraction by ethyl acetate as indicated by Bourquelot. They obtained a grayish powder which did not present the characteristics of the taxicatine. Other unsuccessful extractions made with alcohol and with water led them to the conclusion that "one cannot say positively that the leaves do not contain a glucoside, but the evidence indicates that they do not."

Since the author was working on experiments with *taxus canadensis*, it occurred to him to make comparative studies of *taxus brevifolia*. These are the experiments related below. We used for identification of glucosides the biochemical method of Bourquelot (3, 4).

Two hundred fifty grams of leaves, gathered in January 1939 in the region of Seattle, Washington, were put in boiling alcohol at 80°, to which had been added calcium carbonate, and maintained at boiling point for twenty minutes. The leaves were ground and the treatment, with new alcohol, repeated twice. After filtration of the liquid, it was evaporated under reduced pressure. We had then 280 cc. of solution on which our experiments were made.

We took out 50 cc. and the rest, to which we added 1 cc. of toluol and 2 Gm. of invertase, was placed in an incubator at 30° C.

After defecation of the above-mentioned 50 cc. with 12 cc. of lead acetate, we made an examination with the polarimeter and calculated the reducing sugars by Bertrand's method.

Polarimetric examination: + 20′
Reducing sugars: 0.908 Gm. per 100 cc. of solution.

After 13 days in the incubator, 50 cc. of the solution to which invertase had been added were examined in the same way. The rest was put in a boiling bath for fifteen minutes to destroy the invertase and after the addition of emulsin was replaced in the incubator.

Examination of the 50 cc. gave the following results:

Polarimetric examination: −1° 56′
Reducing sugars: 2.725 Gm. per 100 cc. of solution.

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After seven days, the action of emulsin having ended, the results were as follows:

Polarimetric examination: $-27'$
Reducing sugars: 3.180 Gm. per 100 cc. of solution.

From these results, we can come to the following conclusions. Between the first and second examinations, we have had a change in the rotation corresponding to: $+20' - (-1° 56') = 136'$. At the same time the reducing sugars increased by: 2.725 Gm. − 0.908 Gm. = 1.817 Gm. The number of mg. of reducing matter, expressed in glucose, formed in 100 cc. of solution under the influence of the invertase, shows an index of 801 for a change of deviation of 1°.

Consultation of the table giving the index corresponding to the principal monosaccharids shows that the nearest is 673 for gentianose. The difference between 801 and 673 being rather great, it is plausible to assume the presence of one polysaccharid associated or not with saccharose or with raffinose, the latter having been found in *taxus baccata*. This hypothesis remains to be verified.

If we consider now the second and third examinations, we have a change to the right of the polarimetric rotation equal to: $-1° 56' - (-27') = 89'$. The reducing sugars show an increase of: 3.180 − 2.725 = 0.455 Gm.

The number of mg. of reducing matter, expressed in glucose, formed in 100 cc. of solution under the influence of the emulsin shows an index of 306 for a change of deviation of 1°. The index of the *taxicatine* being 296, we can come to the conclusion that the presence of *taxicatine* is probable and that the study of fermentative action on the product extracted by I. Jones and E. V. Lynn would be able to solve the problem.

NOTE: We are indebted to Dr. F. J. Goodrich of the University of Seattle for procuring for us the leaves of *taxus brevifolia*.

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STANDARDIZED COLOR NAMES FOR DRUGS AND PHARMACEUTICALS.

Following three years of research and experimentation on the Color Names Project, both at the National Bureau of Standards and in the A. PH. A. Laboratory, two major objectives have been achieved. The first consisted of the development of the system of accurate, simple color names in the form of usable charts and the procedures for their application. At its annual meeting in February, the Inter Society Color Council, under whose direction the work is being carried out, approved the color names developed and the techniques for applying them to powders such as the N. F. and U. S. P. powdered drugs and chemicals, and to crude drugs such as leaves, stems and fruits.

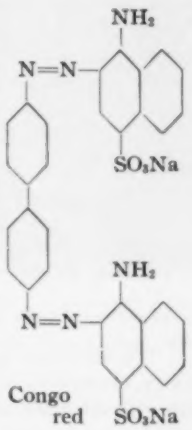
The second objective attained and the first practical result of this study was the recommendation to the N. F. Revision Committee of the list of accurate color names based on this system determined for 100 powdered drugs in the N. F. VI. In like manner, the powdered drugs in the U. S. P. XI are now being studied by the Color Names Committee and it is planned that a similar report covering these drugs will be presented to the U. S. P. Committee of Revision in the spring. The powdered chemicals in both books are also being named according to the same system. The next groups of color names to be studied will be those applied to microscopic structures of vegetable drugs and to solutions. Experience so far gained indicates that the system is so simple that anyone with normal eyesight can apply it.

TOXICOLOGICAL STUDIES ON CONGO RED.*

BY DAVID I. MACHT, WILTON C. HARDEN AND MARY L. GRUMBEIN.

INTRODUCTION.

Congo red, long known as a laboratory reagent, has been used as an indicator for free hydrochloric acid, and as a test for amyloid and for the estimation of the functional state of the reticulo-endothelial system (1, 2). In recent years, however, its use has been extended to therapeutic procedures, and it has been employed empirically in the treatment of pernicious anemia (3), as a hæmostatic agent in cases of pulmonary tuberculosis (4, 5), uterine bleeding (6) and purpura hemorrhagica (7). Although, according to older authorities (8), the dye possesses no bactericidal action, congo red has more recently been advocated in the treatment of streptosepticemia, and in some quarters it is evidently regarded as a chemotherapeutic agent. Thus, for instance, Green (9) advocates injection of 20 cc. of a one per cent solution of congo red on each of three to seven successive days in the treatment of *Streptococcus viridans* septicemia. In connection with such intravenous employment of congo red solutions, further information concerning the potency or toxicity of various samples of the dye obtainable on the market was held by the writers to be very desirable. The present investigation was begun with this object in view and was further stimulated by a few clinical reports of severe collapse and even of sudden death following intravenous injection of congo red administered by physicians who purchased preparations of the dye on the open market. In one such fatal case death was reported to be due to cerebral embolism.



Congo red

EXPERIMENTS ON BLOOD COAGULATION.

Taliaferro and Haag (10) in an excellent monograph on the toxicity and effect of congo red on blood coagulation have reported that injection of small doses of a one per cent solution of the dye (1 to 5 cc. per kilo weight) diminished the coagulation time of rabbits' blood, as determined by a modified capillary glass tube method. When the dye was injected in larger doses, however, they found that the coagulation time of rabbits' blood was markedly delayed. The same authors found further that small doses have no effect on coagulation time of dogs' blood for a period of three hours after injection of the dye. On the other hand, these writers reported that doses of 10 to 15 cc. of a one per cent solution of congo red, administered to ten patients, definitely decreased the blood coagulation time of the majority. In the same paper, Taliaferro and Haag stated that experiments *in vitro* revealed that small amounts of congo red had no effect at all on coagulation time of rabbits' blood.

The present writers have made studies on coagulation time of cats' blood *in vitro* with results quite at variance with those obtained by the previous authors in experiments *in vitro* with rabbits' blood. Tests were made with oxalated blood plasma and blood serum of cats by the well-known Howell-McLean method (11, 12), a procedure which admits of accurate and simultaneous determination of coagulation time of a large number of samples. To a given quantity of the plasma, usually 0.5 cc., is added a little blood serum, usually 0.1 cc., and the onset

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of jellying or clotting is conveniently observed by gently tilting the small glass containers. When the mixture ceases to flow and the tubes can be completely inverted without spilling, the clotting-point has been reached.

Employing the method described above, the authors made numerous experiments in which mixtures of plasma and serum in different proportions were compared with mixtures of plasma with sera in which there had been dissolved various quantities of congo red. Controls were made with physiological saline. Thus it was found that when very dilute solutions of congo red were employed in this manner coagulation time was greatly *shortened*, while that of serum containing greater concentrations of congo red was *prolonged*, and in extreme cases clotting was prevented altogether. The subjoined table summarizes the results obtained in many such experiments. These findings corroborate and extend the conclusions reached by Taliaferro and Haag and emphasize the importance of the concentration of the dye in the blood in relation to coagulation phenomena. Dilute solutions of congo red hasten coagulation time while stronger concentrations delay it. Inasmuch as coagulation time may vary not only with the dose of a thromboplastic drug but also with different species of animals and different individuals of the same species, the question of a safe therapeutic dose must be seriously considered in the case of each patient.

TABLE I. EXPERIMENTS WITH CONGO RED ON COAGULATION OF CATS' BLOOD.

Substance Tested.	Coagulation Time.
0.5 cc. plasma + 0.1 cc. serum with saline (control)	15 minutes
0.5 cc. plasma + 0.1 cc. serum with congo red, 1:500	remained fluid over night
0.5 cc. plasma + 0.1 cc. serum with congo red, 1:5,000	9 minutes
0.5 cc. plasma + 0.1 cc. serum with congo red, 1:50,000	6 minutes

TOXICITY FOR CATS.

To ascertain whether or not different lots of congo red have approximately the same toxicity, the writers procured a number of samples of the dye from the open market and compared them with other samples taken from our own stock, and also with a congo red which had been repurified several times in these laboratories. The pharmacological method of testing toxicity may be described as follows: A one per cent solution of the dye was prepared in normal physiological sodium chloride. This was injected at regular intervals, 1 to 5 cc. at a time, into the femoral vein of cats under light ether anesthesia. Simultaneously a continuous record of the respiration and blood pressure was made on a kymograph. Table II shows the figures obtained with five different lots of the dye. Thus in Lot A the average lethal dose was 320 mg., a figure agreeing with that obtained by Taliaferro and Haag in experiments on rabbits. This particular preparation was a quantity of congo red which had been repurified chemically several times in these laboratories according to the method suggested by Kolthoff (13). Chemical analysis showed that its purity was approximately 95 per cent. The hydrogen-ion concentration of this solution was 7.1. The other samples of congo red which were tested gave readings varying all the way from 102 to 270 mg. per kilo weight of cats. The writers found that the toxicity of a given sample of the dye was but little affected by variations in the hydrogen-ion concentration, *provided* it was on the alkaline side or close to the neutral point. The most interesting finding, however, was the great difference in toxicity of the five different samples of congo red which were repeatedly examined.

TABLE II. TOXICITY OF CONGO RED FOR CATS ON INTRAVENOUS INJECTION.

Lot.	Number of Cats Used.	p_H	Average Lethal Dose Per Kilo.	Remarks.
A	6	7.1	320 mg.	Repurified several times
B	6	6.9	225 mg.	Not repurified
C	4	6.8	102 mg.	Impure sample
D	4	10.5	270 mg.	Large quantities of sodium chloride and 3% of sodium sulfate
E	4	9.5	120 mg.	Large quantities of sodium chloride and traces of sodium sulfate

In a number of the cats used for assay (not listed in Table II) death occurred suddenly after injection of but smal quantities of congo red, *i. e.*, much less than the usual lethal dosage. Such

animals exhibited a phenomenon not unlike that encountered in blood pressure experiments with cats when a clot is formed in the cannulated artery. Post mortem examination in these cases, however, revealed no clot in the cannula itself and the reason for sudden death could not be definitely learned. Nevertheless such findings did not oppose the assumption that intravascular clotting had occurred in the cerebral circulation because the sudden arrest of respiration followed by fall in blood pressure was exactly like that noted in animals with embolism produced by intravenous injection of either oil or solid particles. Unfortunately the writers were not in a position to confirm this hypothesis by actual histological examination.

Some support was lent to this hypothesis by the findings made by the writers in other experiments in which the animals were injected with heparin (H. W. & D.) and the lethal dosage of congo red was determined by the method outlined above. In such tests it was generally found that the toxicity of the dye was definitely decreased when heparin had been previously administered. Figures 1 and 2 illustrate the effect produced by injection of a one per cent solution of the same sample of congo red in two cats, one of which received the saline solution of the dye alone while the other was previously given an effective dose of heparin.

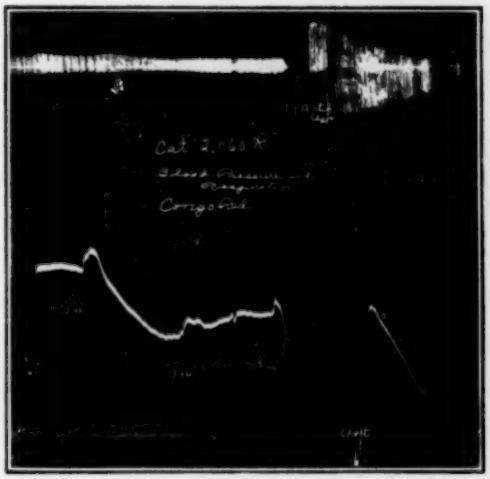

Fig. 1.—Sudden death after injection of 12 cc. of a solution of congo red, 1 per cent, with a picture of intravascular clotting.

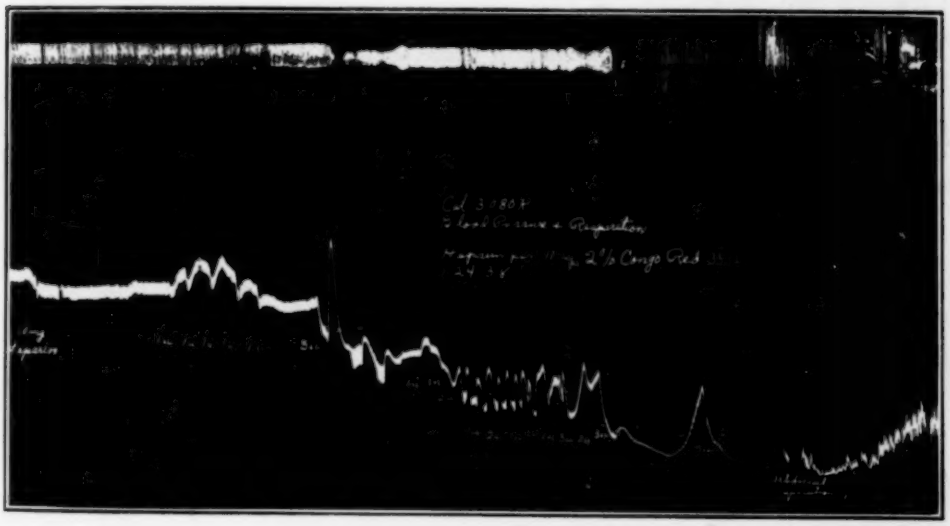

Fig. 2.—Injection of 12 cc. of a solution of the same lot of congo red, 2 per cent, after administration of 10 mg. of heparin.

TOXICITY FOR MICE.

The great difference in toxicity of various samples of congo red observed in over forty experiments on cats intravenously injected with respective solutions of the dye was also exhibited in the series of tests on white mice, injected intraperitoneally or subcutaneously or in the tail

vein. It was found that the lethal intraperitoneal dose for mice averaging 24 Gm. in weight varied with the different samples. Lethal doses per mouse ranged from 5 to 10 mg., depending on the lot of dye employed, but were virtually uniform for any given lot. In other series of experiments, small doses (1 to 3 mg. per mouse) of congo red were given intraperitoneally daily and it was found that with repeated injection even of small doses, chronic poisoning occurred, ending in death after several days. In such tests, heparin previously injected exerted no antidotal action.

DISCUSSION.

The present investigation yielded two principal findings. *First*, a striking difference in toxicity of the various lots of congo red for both mice and cats was noted. This toxicity is due partly to the intrinsic property of the congo red molecule itself, as the results obtained with repurified dye indicate, but it is greatly increased by the presence of impurities. Although some of the samples, such as Lot E, contained huge quantities of sodium chloride and sodium sulfate, the authors did not regard the presence of these salts *per se* as explanatory of the marked toxicity of the respective solutions.

Secondly, the finding made by Taliaferro and Haag in their studies on the effect of congo red on the coagulation of blood has been extended. The writers have found in experiments *in vitro* that congo red in great dilution hastens coagulation of cats' blood whereas the stronger concentrations of the dye may not only retard coagulation but even keep the blood permanently fluid. Whether these findings cast any light on the severe reactions occasionally encountered in patients injected with congo red cannot be positively asserted. Yet on the basis of the data already in hand, a word of caution with regard to the intravenous use of congo red may not be out of place. In the first place, in the case of such a complicated chemical as a dye, it is desirable to employ a preparation as nearly pure chemically as possible. In the second place, before administering the dye, the wise physician will recall the thromboplastic effects of congo red noted in animal experiments both *in vivo* and *in vitro*. The safest concentration to use must be determined by the physician in each individual case. The possibility of combining an anticoagulant such as heparin should also be considered in certain instances.

SUMMARY.

1. The effect of congo red on coagulation of cats' blood depends on the concentration of the dye employed, small doses of the drug hastening coagulation and large doses delaying it, according to experiments made *in vitro*.

2. The toxicity of various samples of congo red, obtained on the market, varies widely for both mice and cats.

3. In connection with clinical injections of congo red, only the purest brands of the dye should be employed and the possibility of a thromboplastic effect should be borne in mind in the case of each patient.

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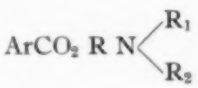
A SERIES OF CONTRIBUTIONS TO THE QUESTION OF THE RELATION BETWEEN CHEMICAL CONSTITUTION AND LOCAL ANESTHETIC ACTIVITY.

III. SUBSTITUTED CINNAMIC ACID ESTERS OF DIALKYLAMINO ALCOHOLS.

BY W. A. LOTT AND W. G. CHRISTIANSEN.

The first paper in this series dealt with the mechanism by which local anesthetics act and with hypotheses developed for use in orienting our efforts to produce new local anesthetics superior in one respect or another to existing ones. Particular emphasis was placed on the question of dual emulsions—systems which have water-in-oil and oil-in-water emulsions in equilibrium with each other and which can be altered or displaced in one direction or another by substances entering the system and having oil solubility as well as water solubility. Such substances would distribute themselves in accordance with their solubility coefficients and in so doing would alter the complex emulsion system. It is reasonable to expect that structural changes sufficient to significantly alter the oil solubility of a compound would modify the properties of the compound in so far as it is involved in complex emulsion systems.

Local anesthetics of the type studied in these researches may be represented by a general formula such as the following:



in which Ar represents an aromatic nucleus, R represents a polymethylene or substituted polymethylene group and R_1 and R_2 represent alkyl or substituted alkyl groups. These compounds may be described as esters obtained from aromatic acids and substituted amino alcohols. By appropriately altering the character of the acid or the alcohol one can change the oil-water solubility relationships.

The second paper was a report on anesthetics derived from alkoxy-benzoic acids. The character of the alkoxy group and other substituents in the benzene ring as well as the structure of the alkylaminoalkyl group were varied so as to produce substances having different distribution coefficients between oily and aqueous liquids and permit selection of the optimum combination of the acidic and alcoholic components.

It has long been known that the aromatic acid used for the preparation of a local anesthetic may be a cinnamic acid instead of a benzoic acid indicating that

in so far as local anesthetics are concerned the $C_6H_5CH = CH-$ nucleus is qualitatively equivalent to the C_6H_5- nucleus. The cinnamic nucleus offers an excellent opportunity to study the effect of substitution, of the kind which would be expected to cause significant change in oil-water solubility relationships, on the behavior of the compounds as anesthetics. Thus, in addition to the benzene ring, the alpha and beta carbon atoms are available for the introduction of substituents. And whereas substitutions in the benzene ring are essentially the same in both the benzoate and cinnamate series so that in this respect the latter does not offer any opportunities fundamentally different from those found in the benzoate series, the possibility of substitution on the alpha and beta carbon atoms provided in the cinnamate series does not exist in the benzoate series. We are, therefore, able by working in the cinnamate series to study a factor which could not be investigated in the benzoate series. Consequently much of our work on the cinnamates has been directed toward determining the effect of substitution on the alpha and beta carbon atoms. By introducing alkyl groups at this point and gradually increasing the size of the alkyl substituent, one can appreciably change the oil solubility of the compound and do it gradually.

The compounds studied in the present work can be represented by the following formula:

$$C_6H_5CH = \underset{\displaystyle R}{\overset{\displaystyle |}{C}} - COOC_2H_4N(C_2H_5)_2 . HCl$$

$$C_6H_5CH = \underset{\displaystyle R}{\overset{\displaystyle |}{C}} - CONH . C_2H_4N(C_2H_5)_2 . HCl$$

R has been varied so that it has represented methyl, ethyl, propyl (both normal and iso), normal butyl and normal amyl. This covers a wide range and we have found that the lengthening of the group brings about a progressive increase in anesthetic potency and this is attributable to the increase in the organotropic portion of the molecule.

A number of analogous compounds were prepared in which the alkyl above designated by R was on the beta carbon. This did not influence the anesthetic activity very greatly. Neither did substitution in the ring by either $-Cl$, $-N(CH_3)_2$ or $-NH_2$.

Among the new compounds are:

(*a*) seven β-diethylaminoethyl α-alkyl-cinnamates.
(*b*) four ring substituted dialkylaminoalkyl α-ethyl-cinnamates.
(*c*) two β-diethylaminoethyl β-alkyl-cinnamates.
(*d*) five *N*-(β-diethylaminoethyl)-α-alkyl-cinnamamides.

In every instance the compounds had pronounced local anesthetic activity. The details of their pharmacological evaluation will be reported shortly in separate publications emanating from the Biological Laboratories of E. R. Squibb and Sons and from the Department of Pharmacology, University of Nebraska, Medical School.

EXPERIMENTAL.

Preparation of α-Alkyl-Cinnamic Acids.—These substances were prepared by the Claisen condensation (1) in which an ester was condensed with benzaldehyde, or substituted benzaldehyde in the presence of sodium

$$C_6H_5CHO + \underset{\underset{C_2H_5}{|}}{CH_2COOCH_3} \longrightarrow C_6H_5CH = \underset{\underset{C_2H_5}{|}}{C} - COOCH_3$$

and the resulting α-alkyl-cinnamic ester hydrolyzed to give the free acid.

Preparation of β-Alkyl-Cinnamic Acids.—These acids were prepared by the Reformatsky synthesis (2) in which the appropriate homolog of acetophenone was condensed with ethyl bromo acetate in the presence of zinc wool.

$$\underset{\underset{CH_3}{|}}{C_6H_5C} = O + CH_2Br.COOC_2H_5 \longrightarrow \underset{\underset{CH_3}{|}}{C_6H_5C(OH)}.CH_2COOC_2H_5$$

and the result β-hydroxy-β-alkyl-β-phenyl-propionic ester saponified to give the free acid. This acid was then dehydrated by means of concentrated sulfuric acid to give the corresponding β-alkyl-cinnamic acid.

$$C_6H_5.\underset{\underset{CH_3}{|}}{C(OH)}.CH_2COOH \longrightarrow \underset{\underset{CH_3}{|}}{C_6H_5C} = CH.COOH$$

Preparation of Diethylaminoethyl α-Alkyl-Cinnamate Hydrochlorides.—Two methods were employed in the preparation of these anesthetic esters.

Method A.—The α-alkyl-cinnamic acid was converted to the corresponding acid chloride and the latter was digested with an equimolecular quantity of the diethylaminoethanol in an inert solvent. In those instances when the hydrochloride of the ester crystallized out of the solvent upon standing, it was purified by recrystallizing directly from a suitable solvent. However, when spontaneous crystallization of the product did not occur, the hydrochloride of the ester and any unreacted amino alcohol were extracted from the reaction solvent by means of acidulated water. The bases were then liberated by alkalinizing the aqueous solution. An ether solution of the liberated bases was then washed repeatedly with water to remove the diethylaminoethanol. Then, after thoroughly drying the ether solution by means of anhydrous potassium carbonate, the hydrochloride of the ester was precipitated by the addition of an ethereal solution of anhydrous HCl. This product was then recrystallized from a suitable solvent.

Method B.—The sodium salt of the α-alkyl-cinnamic acid was digested with diethylaminoethyl chloride in alcoholic solution. After the precipitated sodium chloride had been removed by filtration, the alcoholic solution was concentrated and the hydrochloride of the ester precipitated by the addition of an ethereal solution of hydrogen chloride. Purification of the product was effected by recrystallization from a suitable solvent.

Preparation of β-Diethylaminoethyl β-Alkyl-Cinnamate Hydrochlorides.—Method C.—The β-diethylaminoethyl β-alkyl-cinnamate hydrochlorides were all prepared by a method exactly analogous to the above mentioned *A*.

Preparation of β-Diethylaminoethyl α-Alkyl-Cinnamamide Hydrochlorides.—Method D.—The β-diethylaminoethyl α-alkyl-cinnamamide hydrochlorides were prepared by digesting the α-alkyl-cinnamyl chloride with unsymmetrical diethyl ethylene diamine in an inert solvent. The product was isolated and purified in a manner exactly analogous to the above method *A*.

In Table I the eighteen new compounds are enumerated and the methods used for their preparation and purification indicated. Characterizing physical and chemical data for each individual is also presented therein.

TABLE I.

Dialkylaminoalkyl α-Alkyl-Cinnamate Hydrochloride.	Method.	M. P., °C.	Solvent.	Formula.	Analyses, %. N. Calcd.	N. Found.	Cl. Calcd.	Cl. Found.
β-Diethylaminoethyl (α-methyl)	A	133–134.5	Acetone	$C_{16}H_{24}O_2NCl$	4.70	4.90	11.91	11.57
β-Diethylaminoethyl (α-ethyl)	A, B	145	Acetone-Abs. EtOH	$C_{17}H_{26}O_2NCl$	4.49	4.32	11.38	11.57
γ-Diethylaminopropyl (α-ethyl)	A	143.8–144.4	Benzene	$C_{18}H_{28}O_2NCl$	4.30	4.23	10.89	10.86
β-Diethylaminoethyl (α-n-propyl)	A	125–126	Acetone-Ether	$C_{18}H_{28}O_2NCl$	4.30	4.54	10.90	10.80
β-Diethylaminoethyl (α-isopropyl)	B	152–153	Benzene	$C_{18}H_{28}O_2NCl$	4.30	4.63	10.90	10.96
β-Diethylaminoethyl (α-n-butyl)	B	105.5–106.5	Acetone	$C_{19}H_{30}O_2NCl$	4.12	4.16	10.44	10.29
β-Diethylaminoethyl (α-n-amyl)	B	83–85	Acetone	$C_{20}H_{32}O_2NCl$	3.96	4.26	10.03	10.07
Ring Substituted Dialkylaminoalkyl α-Alkyl-Cinnamate Hydrochloride								
β-Diethylaminoethyl (α-ethyl)-o-chloro	A	127.5–128	Acetone	$C_{17}H_{25}O_2NCl_2$	4.04	4.32	10.25	9.72
β-Diethylaminoethyl (α-ethyl)-p-dimethylamino	B	170–171	Acetone-Abs. EtOH	$C_{19}H_{31}O_2N_2Cl$	7.87	7.95	9.97	9.35
γ-Diethylaminopropyl (α-ethyl)-p-amino	A	191–192	Abs. EtOH-Ether	$C_{18}H_{30}O_2N_2Cl_2$	7.42	7.54	18.80	18.80
γ-Diethylaminopropyl (α-ethyl)-o-amino	A	170–170.5	Abs. EtOH-Ether	$C_{18}H_{30}O_2N_2Cl_2$	7.42	..	18.80	18.80
Dialkylaminoalkyl (β-Alkyl)-Cinnamate Hydrochloride								
β-Diethylaminoethyl (β-methyl)	C	141–142	Abs. EtOH	$C_{16}H_{24}O_2NCl$	4.70	4.85	11.91	11.93
β-Diethylaminoethyl (β-propyl)	C		.....	$C_{18}H_{28}O_2NCl$	4.30	4.94	10.90	10.33
***N*-(Dialkylaminoalkyl) (α-Alkyl)-Cinnamamide Hydrochloride**								
N-(β-Diethylaminoethyl)-(α-methyl)	D	111–112.5	Acetone-Benzene	$C_{16}H_{25}ON_2Cl$	9.44	9.62	11.95	11.84
N-(β-Diethylaminoethyl)-(α-n-propyl)	D	134.2–134.9	Methyl-Ethyl Ketone	$C_{18}H_{29}ON_2Cl$	8.62	8.71	10.92	10.89
N-(β-Diethylaminoethyl)-(α-ethyl)	D	163–164	Abs. EtOH	$C_{17}H_{27}ON_2Cl$	9.02	9.11	11.41	11.46
N-(β-Diethylaminoethyl)-(α-n-butyl)	D	124.5	Acetone	$C_{19}H_{31}ON_2Cl$	8.27	8.62	10.47	10.25
N-(β-Diethylaminoethyl)-(α-amyl)	D	92–95	.....	$C_{20}H_{33}ON_2Cl$	7.94	8.00	10.05	9.97

SUMMARY.

1. A series of compounds derived from α-alkyl- and β-alkyl-cinnamic acids designed to be local anesthetics were prepared. Included were:

β-diethylaminoethyl α-alkyl-cinnamate hydrochlorides.

β-diethylaminoethyl β-alkyl-cinnamate hydrochlorides.

N-(β-diethylaminoethyl)-α-alkyl-cinnamamide hydrochlorides.

2. These compounds have all proved to be potent local anesthetics in pharmacological tests and the details of these studies are to be presented shortly.

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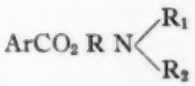
A SERIES OF CONTRIBUTIONS TO THE QUESTION OF THE RELATION BETWEEN CHEMICAL CONSTITUTION AND LOCAL ANESTHETIC ACTIVITY.

IV. LOCAL ANESTHETICS CONTAINING AN EPHEDRINE-LIKE NUCLEUS.

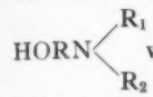
BY W. A. LOTT AND W. G. CHRISTIANSEN.

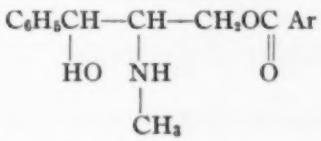
Researches described in Parts II and III of this series have dealt primarily with the acidic component of local anesthetics—the term acidic as used here refers

to the portion of the molecule designated as $ArCO_2$—in the following general formula:

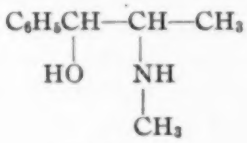


The research now being reported relates to the alcohol component, namely, the

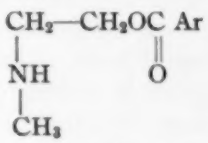
 which is esterified with a suitable acid. It was thought that by so adjusting the configuration of the alcohol that it would bear some structural resemblance to ephedrine, it might be possible to obtain anesthetics possessing vasopressor activity as well. It was our initial aim to prepare an anesthetic ester corresponding to the following formula:



It will be noted from the following formula for ephedrine and an anesthetic ester that the above represents a combination of these two types of structures:

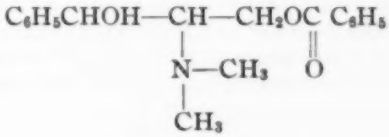


Ephedrine

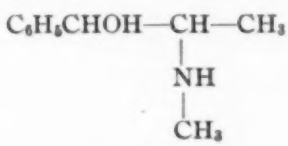


Anesthetic ester

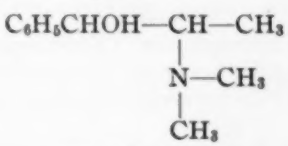
The attempts to produce this substance failed and for reasons of chemical feasibility it was decided to prepare the analogous dimethyl amino compound having the following formula:



This was done in full realization of the fact that the pressor activity of a tertiary amino body is expected to be less than that of a secondary amino body. Thus, *N* methylated ephedrine has less pressor activity than ephedrine,

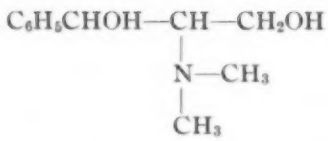


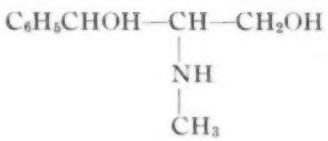
Ephedrine



N-Me Ephedrine

and, similarly, the following tertiary amino alcohol would be expected to have less pressor activity than the corresponding secondary amino alcohol.





It was hoped, however, that the 1-phenyl-2-dimethylamino-1,3-propanediol 3-monobenzoate hydrochloride and analogous esters might still exhibit discernible pressor activity, or possibly some qualitatively different advantages, and a series of such esters was prepared.

The series successfully synthesized included:

1. 1-Phenyl-2-dimethylamino-1,3-propanediol 3-monobenzoate hydrochloride.
2. 1-Phenyl-2-diethylamino-1,3-propanediol 3-monobenzoate hydrochloride.
3. 1-Phenyl-2-diethylamino-1,3-propanediol 3-mono-α-ethyl-cinnamate hydrochloride.
4. 1-Phenyl-2-diethylamino-1,3-propanediol 3-monocarbanilate hydrochloride.
5. 1-Phenyl-2-diethylamino-1,3-propanediol 3-mono-*p*-ethoxy-benzoate hydrochloride.
6. 3-Phenyl-3-methoxy-2-diethylaminopropyl-monocarbanilate hydrochloride.

All of these compounds proved to be potent local anesthetics in preliminary pharmacological tests. Although in several instances blanched areas about the site of injection were observed, no vasopressor activity was observable in actual blood pressure measurements. The pharmacological results will be published separately in publications emanating from the Biological Laboratories of E. R. Squibb and Sons, and the Department of Pharmacology, University of Nebraska, Medical School.

EXPERIMENTAL.

Preparation of Dialkyl Amino Alkanols.—The substituted amino alkanols were made essentially according to the methods described by Cherbuliez (1) and Beaufour (2). Thus, 1-phenyl-2-diethylamino-1,3-propanediol was prepared by adding the elements of hypobromous acid to cinnamic alcohol to form the corresponding bromohydrin, and then treating with diethylamine to replace the bromine with a diethylamino group.

$$C_6H_5{-}CH{=}CH{-}CH_2OH + HOBr \longrightarrow C_6H_5{-}CHOH.CHBr.CH_2OH$$
$$C_6H_5{-}CHOH{-}CHBr.CH_2OH + (C_2H_5)_2NH \longrightarrow C_6H_5{-}CHOH.CHN(C_2H_5)_2.CH_2OH + HBr$$

DIALKYL AMINO ALKANOLS.

Substance.	B. P. ° C.	Mm.	Formula.	N Analyses, %. Calcd.	Found.
1-Phenyl-2-diethylamino-1,3-propanediol	149–150[a]	2	$C_{13}H_{21}O_2N$	6.27	5.96
3-Phenyl-3-methoxy-2-diethylamino-1-propanol	128–133	4	$C_{14}H_{23}O_2N$	5.90	..
1-Phenyl-2-dimethylamino-1,3-propanediol	150–157	4	$C_{11}H_{17}O_2N$	7.17	7.18

[a] The B. P. recorded by Cherbuliez is 175–178° C. (14 mm.).

1-Phenyl-2-Diethylamino-1,3-Propanediol 3-Benzoate Hydrochloride.—To a chilled solution of 24.5 Gm. of 1-phenyl-2-diethylamino-1,3-propanediol dissolved in 50 cc. of anhydrous benzene was added 15.6 Gm. of benzoyl chloride dissolved in 50 cc. of anhydrous benzene. Twenty cubic

centimeters of dry ether was added to the reaction mixture which then upon standing tightly stoppered over night in the ice box deposited a crop of white crystals of the hydrochloride. The product was drained on a Buchner funnel and washed with cold solvent. Two crystallizations from alcohol and ether with one decolorizing treatment with charcoal resulted in 27.4 Gm. of product of constant melting point 181–181.5° C.

Anal. Calcd. for $C_{20}H_{26}O_3NCl$: N, 3.85; Cl, 9.75
Found: N, 3.61; Cl, 9.75

1-Phenyl-2-Diethylamino-1,3-Propanediol 3-α-Ethyl-Cinnamate Hydrochloride.—4.4 Gm. of α-ethyl-cinnamylchloride dissolved in 25 cc. of anhydrous ether was added to 4.6 Gm. of 1-phenyl-2-diethylamino-1,3-propanediol dissolved in 60 cc. of anhydrous ether. After refluxing 6 hours then chilling and diluting the reaction mixture with ether a crystalline product was obtained which upon crystallization from alcohol had a melting point of 149–150° C.

Anal. Calcd. for $C_{24}H_{32}O_3NCl$ Cl, 8.49; N, 3.35
Found: Cl, 8.83; N, 3.78

1-Phenyl-2-Diethylamino-1,3-Propanediol 3-Mono-Carbanilate Hydrochloride.—7.8 Gm. of phenylisocyanate dissolved in 40 cc. of dry benzene was added dropwise to 14.6 Gm. of 1-phenyl-2-diethylamino-1,3-propanediol dissolved in 40 cc. of dry benzene. The reaction mixture, tightly stoppered, was allowed to stand at room temperature several days then rendered just acid to Congo red paper with ethereal hydrogen chloride. The product which separated was crystallized from acetone. Seventeen grams were obtained with melting point 203–204° C.

Anal. Calcd. for $C_{20}H_{25}O_3N_2Cl$: N, 7.40; Cl, 9.36
Found: N, 7.34; Cl, 9.65

1-Phenyl-2-Diethylamino-1,3-Propanediol 3-Mono-p-Ethoxy-Benzoate Hydrochloride.—To 5.5 Gm. of 1-phenyl-2-diethylamino-1,3-propanediol, b. p. 175–190° C. (13 mm.), dissolved in 25 cc. of anhydrous benzene was added a solution of 4.2 Gm. of *p*-ethoxybenzoyl chloride in 25 cc. of anhydrous benzene and the reaction mixture refluxed for six hours. The benzene was then removed by distillation and the residue recrystallized from absolute alcohol. The product obtained amounted to 2.4 Gm., m. p. 177–178° C.

Anal. Calcd. for $C_{22}H_{30}O_4NCl$: N, 3.51; Cl, 8.90
Found: N, 3.64; Cl, 8.10

3-Phenyl-3-Methoxy-2-Diethylaminopropyl-Mono-Carbanilate Hydrochloride—5.2 Gm. of phenylisocyanate dissolved in 25 cc. of anhydrous ether was added to 9.3 Gm. of 2-diethylamino-3-phenyl-3-methoxy-1-propanol, b. p. 128–133° C. (4 mm.), dissolved in 20 cc. of anhydrous ether. The reaction mixture was refluxed four hours under anhydrous conditions then treated until acid to Congo red paper with ethereal hydrogen chloride. The crystalline product obtained from one crystallization from absolute alcohol had a melting point of 198–199.5° C.

Anal. Calcd. for $C_{21}H_{29}O_3N_2Cl$: Cl, 9.03; N, 7.13
Found: Cl, 9.20; N, 7.09

1-Phenyl-2-Dimethylamino-1,3-Propanediol 3-Mono-Benzoate Hydrochloride.—3.8 Gm. of benzoyl chloride dissolved in 50 cc. of anhydrous benzene was added to 5.1 Gm. of 1-phenyl-2-dimethylamino-1,3-propanediol, b. p. 150–157° C. (4 mm.) dissolved in 50 cc. of anhydrous benzene. The reaction mixture was refluxed fifteen hours and the crystalline product obtained was recrystallized from absolute alcohol, m. p. 215–216° C.

Anal. Calcd. for $C_{18}H_{22}O_3NCl$: N, 4.17; Cl, 10.57
Found: N, 4.18; Cl, 10.63

SUMMARY.

1. A series of 6 new local anesthetics derived from an ephedrine-like amino alcohol were prepared.

2. All of these compounds were potent local anesthetics but showed no measurable vasopressor action.

REFERENCES.

(1) Cherbuliez, Neumeier and Lorenz, *Helv. Chim. Acta*, 14, 186 (1931).

(2) Beaufour, *Bull. soc. chim.* (4), 11, 648 (1912); cf. also *Bull. soc. chim.* (4), 13, 349 (1913); (4), 14, 354 (1913).

STUDIES IN THE EXTRACTION OF CINCHONA.*

BY ADLEY B. NICHOLS[1] AND C. B. SHAH.

The experiments which are recorded in this report were undertaken primarily for the purpose of obtaining specific facts relative to extraction in general and to the extraction of cinchona in particular, because it was known to offer numerous extraction difficulties and because, being an alkaloidal drug, it presented an opportunity for basing the study upon something more tangible and of more relative importance than so-called extractive matter, which might or might not be indicative of drug activity and extraction efficiency.

Reports of other workers and the results of this study indicate that each drug must be considered as a specific problem and that what proves of value in one instance may be utterly lacking in another. Studies of the literature and the results of this study on cinchona bear evidence of both of these conditions. Consequently the results as here reported may or may not be indicative of what might be found with other drugs under similar conditions.

A carefully selected whole red cinchona bark was used in this study. The bark was ground to meet the specifications of numbers 10, 20, 40, 60 and 100 powders, and assays upon these showed the presence of 7.524, 7.436, 7.600, 7.416 and 6.872 per cent of alkaloids of cinchona, respectively.

Due to the nature of the experiments, U. S. P. alcohol was selected as the menstruum throughout, since a multiple-phase menstruum would not have worked satisfactorily under certain conditions and comparative results could not have been obtained unless a uniform menstruum was used in all cases.

EXPERIMENTAL PROCEDURE.

I and II.—To study the effects of vacuum and agitation on extraction in relation to the degree of comminution of the drug, the following maceration experiments were conducted with powders Nos. 10, 20, 40, 60 and 100: (*a*) vacuum but no shaking; (*b*) vacuum with shaking; (*c*) no vacuum and no shaking (plain maceration); (*d*) no vacuum but with shaking (plain maceration with shaking). Each of the experiments was performed in duplicate, and flasks of similar shape and size were used.

The experiments with vacuum were carried out in 250-cc. conical suction flasks whereas those without vacuum were made in similar, plain, conical flasks. Twenty grams of accurately weighed powder were placed in each flask. The suction flasks were closed with stoppers, each carrying a separatory funnel, the side arm of the flask was connected with the vacuum line and 100 cc. of alcohol were placed in the separatory funnel. The dry powders in the flasks were first subjected to a vacuum of 27 inches and maintained under such conditions for ten minutes; then the vacuum connection was closed and sufficient of the alcohol from the funnel was allowed to

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* From a graduate thesis presented by C. B. Shah to the Philadelphia College of Pharmacy and Science.

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enter the flask by opening the cock until the powder was completely covered, a small part of the alcohol being allowed to remain in the funnel so as not to break the vacuum. The powder and the alcohol in each flask were mixed by gentle rotation of the flask and allowed to stand for five minutes. Then the remaining alcohol from the funnel was allowed to pass into the flask and the vacuum was broken. In the experiments without vacuum, after putting the powders into the flasks, 100 cc. of alcohol were added and mixed with the powder by gentle rotation. All of the flasks were then tightly stoppered and the powder was allowed to macerate for one hour. The flasks of the experiments in which the shaking was used, were, after half an hour, placed on a mechanical agitator and shaken for the remaining half hour. The flasks of the experiments with no shaking were, at intervals of fifteen minutes, *i. e.*, three to four times during the experiment, gently rotated for momentary mixing of the contents. At the end of the hour, after shaking the flasks, about 50 cc. of the liquid was decanted through a filter paper and analyzed for both extractive and total alkaloids. In all cases alkaloidal analysis was carried out by the U. S. P. method. The results are given in Tables I to III.

TABLE I.—PER CENT OF EXTRACTIVE MATTER IN THE EXTRACT BY PLAIN AND VACUUM MACERATION, WITH AND WITHOUT SHAKING.

Powder No.:		10.	20.	40.	60.	100.
A. Vacuum, no shaking	I	1.3425	1.956	2.214	3.178	3.110
	II	1.3525	1.946	2.206	3.248	3.118
Average		1.3475	1.951	2.210	3.213	3.114
B. Vacuum, with shaking	I	1.3650	1.904	2.398	3.348	3.076
	II	1.3175	1.834	2.376	3.346	3.002
Average		1.3413	1.869	2.387	3.347	3.039
C. No vacuum, no shaking	I	1.2125	1.772	2.328	3.196	3.126
	II	1.2350	1.814	2.358	3.242	3.098
Average		1.2238	1.793	2.343	3.219	3.162
D. No vacuum, with shaking	I	1.3300	1.822	2.396	3.312	3.024
	II	1.3275	1.834	2.293	3.266	3.028
Average		1.3288	1.828	2.394	3.289	3.026

TABLE II.—PER CENT OF TOTAL ALKALOIDS IN THE EXTRACT (ALSO EXPRESSED IN PERCENTAGE OF THE TOTAL AVAILABLE ALKALOIDS IN THE PORTION OF DRUG EXTRACTED) BY PLAIN AND VACUUM MACERATION, WITH AND WITHOUT SHAKING.

Powder No.:		10.	20.	40.	60.	100.
A. Vacuum, no shaking	I	0.2450	0.3353	0.3710	0.5215	0.5160
	II	0.2377	0.3365	0.3725	0.5285	0.5180
Average		0.2414	0.3359	0.3718	0.5250	0.5170
Per cent of total available alkaloids		16.04	22.72	24.46	35.40	37.63
B. Vacuum, with shaking	I	0.2450	0.3340	0.4005	0.5370	0.5073
	II	0.2341	0.3120	0.4000	0.5385	0.4993
Average		0.2396	0.3230	0.4003	0.5378	0.5033
Per cent of total available alkaloids		15.92	21.72	26.34	36.26	36.63
C. No vacuum, no shaking	I	0.2215	0.3117	0.3875	0.5260	0.5240
	II	0.2179	0.3145	0.3960	0.5305	0.5233
Average		0.2197	0.3131	0.3918	0.5283	0.5237
Per Cent of total available alkaloids		14.6	21.06	25.78	35.62	38.11
D. No vacuum, with shaking	I	0.2415	0.3246	0.4015	0.5420	0.5080
	II	0.2355	0.3210	0.4055	0.5325	0.5113
Average		0.2385	0.3228	0.4035	0.5373	0.5097
Per Cent of total available alkaloids		15.85	21.71	26.55	36.23	37.10

NOTE.—Alkaloids available from 20 Gm. of powder. From No. 10, 1.505 Gm.; from No. 20, 1.487 Gm.; from No. 40, 1.520 Gm.; from No. 60, 1.483 Gm.; from No. 100, 1.374 Gm. (on the basis of analysis by U. S. P. method).

TABLE III.—GM. OF ALKALOID PER ONE GM. OF EXTRACTIVE (CALCULATED FROM C AND D, TABLES I AND II).

Powder No.:	10.	20.	40.	60.	100.
C	0.18	0.175	0.167	0.164	0.166
D	0.18	0.177	0.169	0.163	0.168

From these results it appears that the degree of comminution of the drug is of great importance in the effects of vacuum and shaking on extraction. Whereas vacuum maceration has helped somewhat in powders Nos. 10 and 20, *i. e.*, coarser powders, it has shown no advantage in extraction of powders Nos. 40, 60 and 100.

As regards the effects of mechanical shaking, no better results are shown in conjunction with vacuum in the case of coarse powders (Nos. 10 and 20), although in these powders, without vacuum, it has demonstrated some advantage over plain maceration. In the case of fine powders, however (Nos. 40, 60 and 100), while vacuum did not show any advantage in extraction, mechanical shaking indicates a somewhat more favorable result.

The efficiency of extraction to the degree of comminution of the powder will be seen readily by comparing the results obtained, for instance, in C, Table II. If these results are expressed in such a way that a comparison can be made of the alkaloids extracted (taking the No. 10 powder as the unit) the extraction ratios with powders Nos. 10, 20, 40, 60 and 100 will be 1, 1.44, 1.77, 2.44 and 2.6. That is, due to the size of powder, the No. 60 yields about two and one-half times as much alkaloid as does a No. 10 powder. Therefore it will be seen that the finer the powder the better the extraction, the rate of extraction increasing notably as the size of particle decreases. There is no appreciable difference in the extraction between Nos. 60 and 100 powders, indicating that a No. 60 is the optimum size for the extraction of cinchona.

These results also tend to show that there is no advantage in grinding the powder finer than No. 60, and in the case of this drug at least, the possibility of grinding the drug to such a fine condition as to wash or dissolve the active principles, as in the making of a solution in a single operation, seems to be far remote or at least impractical.

From the results of the effects of vacuum on extraction using the different size powders, it seems that for practical penetration of the solvent, in the case of cinchona, the cells in a No. 40 or finer powder are sufficiently damaged or crushed to allow easy penetration of the solvent, and vacuum offers no added advantage.

The ratio of Gm. of alkaloid per Gm. of extractive, Table III, primarily shows a gradual decrease in the order of the fineness of powder indicating an increase of extractive per Gm. of alkaloid. However, this increase apparently reaches its maximum with No. 60 powder, as No. 100 shows a slight change in the opposite direction. This finding is in line with that of Husa and Huyck (1) who found with belladonna root that the yield of extractive increases as the size of powder decreases down to and including No. 60 powder and that with No. 80 powder there is a decrease in yield of total extractive.

III.—To study the effect of time on the rate of extraction of drug of different degrees of comminution, 20 Gm. of cinchona in Nos. 10, 20, 40 and 60 powders were accurately weighed and placed into 250-cc. conical flasks. One hundred cc. of alcohol were added to each flask and the flasks tightly stoppered. The contents were well mixed by gentle rotation of the flasks for a few minutes and then allowed to macerate, being shaken by gentle rotation for a few minutes at about two-hour intervals, four times during the day. At the end of 24, 48 and 144 hours of such treatment, about 50 cc. of the extracts were filtered and analyzed for extractive and total alkaloids. The results are given in Tables IV to VII.

TABLE IV.—PER CENT OF EXTRACTIVE ON BASIS OF TIME.

Powder No.:	10.	20.	40.	60.
24 hours	2.272	2.688	3.100	3.510
48 hours	2.532	2.924	3.330	3.594
144 hours	2.680	3.114	3.426	3.658

TABLE V. PER CENT OF TOTAL ALKALOIDS BY U. S. P. METHOD, ON BASIS OF TIME.

Powder No.	10.	20.	40.	60
24 hours	0.3680	0.4375	0.4970	0.5455
48 hours	0.4055	0.4580	0.5115	0.5500
144 hours	0.4400	0.4965	0.5585	0.5655

TABLE VI. PER CENT OF TOTAL AVAILABLE ALKALOIDS EXTRACTED (CALCULATED FROM TABLE V).

Powder No.:	10.	20.	40.	60.
24 hours	24.45	29.42	32.70	36.78
48 hours	26.94	30.13	33.65	37.09
144 hours	29.24	33.40	36.74	38.13

TABLE VII.—GM. OF ALKALOID PER ONE GM. OF EXTRACTIVE (CALCULATED FROM TABLES IV AND V).

Powder No.:	10.	20.	40.	60.
24 hours	0.162	0.163	0.160	0.155
48 hours	0.160	0.157	0.154	0.153
144 hours	0.164	0.159	0.163	0.155

These results indicate that within the time limit of six days it does not seem possible to extract the total available alkaloids of the drug by a single maceration, the maximum extraction being about 38 per cent of the available alkaloids.

From Table VI it appears that there is a saturation point at which the rate of extraction tends to remain stationary, such saturation being easily obtained by optimum fineness of the powder in the shorter period of time, coarser powders requiring longer maceration. Thus while powders Nos. 10, 20 and 40 in the initial extraction at one hour (Table II, C) showed percentages of 14.6, 21.06 and 25.78, respectively, these percentages gradually increased with longer maceration until at the end of 144 hours they showed 29.24, 33.40 and 36.74 per cent extraction, respectively. However, with No. 60 powder the increase in extraction with time is not appreciable, increasing from 35.62 per cent in one hour to 38.13 per cent at the end of 144 hours, the saturation point having been quickly attained during the first hour of maceration. Thus it shows that the extraction of cinchona in coarser powders is uneconomical and time-consuming. Powder No. 40, with longer maceration, gives results similar to powder No. 60 and so may be used with advantage where powder No. 60 is found to be too fine for use as in percolation. On the other hand, powders Nos. 10 and 20, *i. e.*, very coarse powders, are unsatisfactory for extraction purposes.

Table VII shows that during the earlier period of maceration the rate of solution of the extraneous matter is greater than that of the alkaloids. However, upon further maceration the ratio of alkaloids to the extraneous matter increases. This finding is in agreement with that of Bull (2), who, by study of the percolation fractions of cinchona, reported that the inert material is extracted more quickly than the alkaloids.

IV.—To study the influence of a single maceration with a large quantity of menstruum, and to note the effects of using the same quantity of the menstruum in divided portions, 20 Gm. of the No. 60 cinchona powder were introduced into a conical flask and 200 cc. of alcohol were added. The flask was then stoppered, the contents well mixed by gentle rotation and allowed to macerate for two hours with frequent agitation. After two hours' maceration, 50 cc. of the extract were filtered and analyzed. Similarly 20 Gm. of cinchona were placed in another flask 100 cc. of alcohol added, the flask stoppered and the contents mixed. After one hour, 80 cc. of the extract were filtered through a Gooch crucible, the residue returned to the flask, and 50 cc. of fresh alcohol added. The flask was stoppered, the contents mixed by gentle rotation, and again after one-half hour 50 cc. of the extract were filtered, the residue returned and the process repeated with another 50-cc. portion of alcohol, finally filtering an additional 50 cc. of the extract. Thus, a total of 200 cc. of alcohol was used. The three fractions of the filtered extract were analyzed and the results are as follows.

The total alkaloids in 200 cc. of the extract obtained by a single maceration amounted to 0.6144 Gm., equivalent to 41.43 per cent of the total available alkaloids.

Total Alkaloids by Fractional Maceration.—0.4292 Gm. in the first extract of 80 cc.; 0.1480 Gm. in the second extract of 50 cc.; 0.0945 Gm. in the third extract of 50 cc.; 0.0378 Gm. estimated as being present in the 20 cc. of menstruum remaining with the marc.

Total.—0.7095 Gm. in 200 cc. of extract obtained by fractional maceration, and equivalent to 47.86 per cent of the total available alkaloids.

These results indicate that for cinchona, in the extraction of the alkaloids by maceration, better results are obtained by maceration with divided portions of menstruum rather than with one single portion of menstruum. Furthermore, in comparison with the results recorded in Table II, C, the extraction of alkaloids by maceration is not directly proportional to the quantity of menstruum used. In Table II, C, for instance, one-hour maceration with 100 cc. of menstruum yielded 35.62 per cent of total available alkaloids while by two hours' maceration with 200 cc. of menstruum the total available alkaloids extracted was increased only to 41.43 per cent.

V.—In order to determine the effect of vacuum and different degrees of comminution of drug by continuous extraction, 10 Gm. of Nos. 10 and 20 cinchona powder were placed in separate flasks and evacuated for ten minutes at 27 inches' vacuum. Fifty cc. of alcohol were added through a separatory funnel carried by the stopper, the contents were mixed and after five minutes the vacuum was broken. After maceration for one hour the contents were transferred to a Soxhlet apparatus, the flasks were rinsed with about 50 cc. of alcohol and extraction over a water-bath was carried on for four hours. A similar set of experiments was performed evacuating the powders for a period of 20 minutes, and extracting in the Soxhlet apparatus for $4^1/_2$ hours. Powders Nos. 10, 20, 40 and 60 were also similarly extracted both for 4 and $4^1/_2$ hours in the Soxhlet apparatus but without evacuation. The results are given in Tables VIII and IX.

TABLE VIII.—TOTAL ALKALOIDS OBTAINED BY EXTRACTION IN THE SOXHLET APPARATUS.

	4 Hours Extraction.		$4^1/_2$ Hours Extraction.	
Powder No.	Alkaloids Obtained from the Extract.	Equivalent Per Cent of the Total Available Alkaloids.	Alkaloids Obtained from the Extract.	Equivalent Per Cent of the Total Available Alkaloids.
10 with vacuum	0.4866 Gm.	64.67%	0.5312 Gm.	70.6 %
20 with vacuum	0.5628 Gm.	75.69%	0.6145 Gm.	82.64%
10 without vacuum	0.5025 Gm.	66.78%	0.5262 Gm.	69.94%
20 without vacuum	0.5292 Gm.	71.17%	0.6252 Gm.	84.08%
40 without vacuum	0.5892 Gm.	77.53%	0.7101 Gm.	93.43%
60 without vacuum*	0.4296 Gm.	.....	0.5341 Gm.	.....

* Powder No. 60 did not show proper extraction as the menstruum did not percolate readily through the powder.

TABLE IX.—TOTAL EXTRACTIVE BY CONTINUOUS EXTRACTION IN THE SOXHLET APPARATUS.

Powder No.	4 Hours Extraction.	$4^1/_2$ Hours Extraction.
10 with vacuum	2.45 Gm.	2.7439 Gm.
20 with vacuum	2.8588 Gm.	3.1523 Gm.
10 without vacuum	2.5819 Gm.	2.7265 Gm.
20 without vacuum	2.7581 Gm.	3.1955 Gm.
40 without vacuum	2.9848 Gm.	3.5797 Gm.

From these results, it appears that extraction of cinchona in very coarse powder is not satisfactory as previously stated. Even vacuum does not seem to offer any advantage under a continuous extraction process, although it seems to be slightly favorable for extraction during a short period of one hour. It appears that the customary procedure of the commercial extraction of drugs by vacuum with coarser powders averaging from Nos. 12 to 16 is not advisable in the extraction of cinchona. Powder No. 40 seems to be practical for percolation or continuous extraction methods even without vacuum. This finding of No. 40 powder as a suitable size for such extraction is in agreement with the findings of Bull (3) in percolation studies of cinchona. He reported that percolation of a moderately fine (44/85) powder gave better extraction of both alkaloids and total solids than either a fine powder No. 85 or a moderately coarse powder (22/60).

VI.—To study the effect of columns of drug of various heights upon extraction by percolation, and also the comparative value of upward (counter-current) extraction, five sets of percolators in duplicate were prepared as follows, each being charged with 50 Gm. of No. 40 cinchona powder.

(A) American type percolator; $^1/_2$ pint capacity; height of powder column about 3 inches; (B) glass tubing of $22^1/_2$ mm. internal diameter; height of powder column about $11^1/_2$ inches; (C) glass tubing of $17^1/_2$ mm. internal diameter; height of the powder column about 21 inches; (D) glass tubing of $11^1/_2$ mm. internal diameter; height of powder column about 43 inches. (E) glass tubing of $17^1/_2$ mm. internal diameter for upward (counter-current) extraction; height of the powder column about 20 inches.

In each case the powder was packed in a dry condition in order to avoid difficulties in packing through narrow tubes, and to make the conditions uniform in all. In set E, the menstruum entered the bottom of the cylinder through a tube attached to the stock container which was

raised to a height of four feet to provide the necessary pressure for a gravity feed. Stoppers, to which glass tubing was attached for delivery of the percolate, were inserted in the tops of the tubes, flush with the powder, providing a solid column of drug. Pinch-cocks at both the bottom and the top served to control the flow of the menstruum and the rate of the percolation.

Sufficient alcohol was poured on top of sets A, B, C and D to moisten and cover the powders completely. In set E alcohol was allowed to enter from below until the drug became saturated, at which time the source of supply was shut off. After allowing the drug to macerate over night, 25 cc. of percolate were collected from each, and thereafter, 25-cc. portions of percolate were collected daily until an equivalent of 200 cc. had been collected The first four fractions of 25 cc. each were analyzed separately for total extractive and alkaloids, and then the additional four fractions of 25 cc. each were combined and similarly analyzed.

The standard percolators (group A) required about 15 minutes for the collection of 25 cc. of percolate. The broadest tubing (set B) required about 25 minutes, the medium tubing (C) took about 60 minutes, the narrowest tubing (D) and the medium tubing (E), upward percolation, about 5 to 6 hours, for the collection of 25 cc. of percolate.

The results of analysis of the various fractions are given in Tables X to XIV.

TABLE X.—TOTAL GM. OF ALKALOIDS IN THE VARIOUS PERCOLATE FRACTIONS.

Fraction:	1.	2.	3.	4.	Combined 5, 6, 7, 8.	Total.
A	0.6770	0.3676	0.2432	0.1795	0.4674	1.9347
(Standard Percolation)	0.5980	0.4288	0.2572	0.1672	0.4494	1.9006
B	0.6660	0.4004	0.2548	0.1571	0.4122	1.8905
(22.5 mm. tubing)	0.5620	0.4316	0.2796	0.1648	0.4374	1.8754
C	0.7370	0.4096	0.2252	0.1528	0.4278	1.9524
(17.5 mm. tubing)	0.6980	0.4488	0.2408	0.1533	0.4170	1.9579
D	0.8360	0.4092	0.1956	0.1509	0.4308	2.0225
(11.5 mm. tubing)	0.9600	0.3317	0.1760	0.1413	0.4368	2.0458
E	0.7360	0.4000	0.2162	0.1509	0.4260	1.9261
(17.5 mm. tubing upward percolation)	0.5690	0.3992	0.2952	0.2021	0.4674	1.9329

TABLE XI.—PER CENT OF ALKALOIDS IN THE VARIOUS PERCOLATE FRACTIONS EXPRESSED IN PER CENT OF TOTAL AVAILABLE ALKALOIDS.

Fraction:	1.	2.	3.	4.	Combined 5, 6, 7, 8.	Total.
A	17.82	9.67	6.40	4.72	12.3	50.91
	15.74	11.28	6.77	4.4	11.83	50.02
B	17.53	10.54	6.71	4.13	10.85	49.74
	14.79	11.36	7.36	4.34	11.51	49.35
C	19.39	10.78	5.93	4.02	11.26	51.4
	18.37	11.81	6.34	4.03	10.97	51.52
D	22.0	10.77	5.15	3.97	11.34	53.22
	25.26	8.73	4.63	3.72	11.49	53.84
E	19.37	10.53	5.66	3.97	11.21	50.74
	14.97	10.51	7.77	5.32	12.30	50.87

TABLE XII.—GM. OF EXTRACTIVE IN THE VARIOUS PERCOLATE FRACTIONS.

Fraction:	1.	2.	3.	4.	Combined 5, 6, 7, 8.	Total.
A	3.7010	2.1680	1.3888	0.9328	2.151	10.3416
	3.6825	2.5648	1.4464	0.7920	1.983	10.4687
B	4.1010	2.3808	1.3376	0.7360	1.887	10.4424
	3.3825	2.4752	1.5984	0.7904	2.043	10.2895
C	4.3130	2.3232	1.1856	0.7792	1.977	10.5780
	4.0015	2.7152	1.3040	0.7712	1.965	10.7569
D	4.8080	2.4784	1.0096	0.6944	1.947	10.9374
	5.7445	1.8416	0.8656	0.6672	1.905	11.0239
E	4.3940	2.3696	1.1472	0.7280	1.944	10.5828
	3.3060	2.3424	1.8400	1.0352	2.202	10.7256

TABLE XIII. PERCENTAGE OF TOTAL AVAILABLE EXTRACTIVE OBTAINED.

	A.	B.	C.	D.	E.
Per cent total available extractive	57.77	58.34	59.10	61.10	59.12
	58.48	57.48	60.09	61.59	59.92

The figures in Table XIII represent the percentage of the total available extractive obtained in the various percolation processes. The total available extractive was derived from the results obtained by use of the Soxhlet apparatus, being in the proportion of 17.9 Gm. per 50 Gm. of drug (see Table IX).

TABLE XIV.—GM. OF ALKALOIDS PER 1 GM. OF EXTRACTIVE (CALCULATED FROM TABLES X AND XII) OF THE FIRST PERCOLATE FRACTION AND OF THE COMBINED 5, 6, 7 AND 8 FRACTIONS.

Fraction:	1.	Combined 5, 6, 7, 8.
A	0.183	0.217
	0.162	0.227
B	0.162	0.218
	0.166	0.214
C	0.171	0.216
	0.174	0.212
D	0.174	0.221
	0.167	0.229
E	0.168	0.219
	0.172	0.212

The results of these experiments show that for practical extraction of cinchona the usual method of percolation with standard percolators is quite satisfactory. The long column tube-type of percolator as is adopted in diacolation and its modified forms, either in downward or upward percolation and even with the rate of percolation as slow as about one drop per minute, offers no appreciable advantage in the continuous extraction of the drug to exhaustion. Of course if the first fraction or two of a percolate is considered, the slow extraction in the taller columns gives somewhat better results than is obtained by the ordinary percolator (15 to 18 per cent by ordinary percolators as compared to 22 to 25 per cent by the tallest columns and slowest percolation, sets A and D, Table XI). Subsequently, however, this advantage decreases and all types tend to similarity upon continued extraction (50 to 51 per cent as compared to 53 to 54 per cent, Table XI, A and D). This shows that there is no particular advantage in such methods over the usual type of percolator when percolation is carried to complete exhaustion of the drug. This can be explained by assuming that even though the long-column diacolation-type method of extraction helps in the earlier stages to dissolve the surface constituents, the final rate of extraction by outward diffusion from within the drug tissues is not different.

Results from Table XIV show that the ratio of alkaloid to the extractive matter gradually increases in progressive fractions of percolate. Non-alkaloidal extractive dissolves more readily than the alkaloids themselves which is in confirmation of an earlier statement concerning maceration. However, although the extractive matter is more readily removed than the alkaloids, for complete extraction there is not a great amount of difference between the removal of alkaloids and extractive matter, 58 to 62 per cent of total available extractive (see Table XIII) as compared to 50 to 54 per cent of total available alkaloids (see Table XI).

SUMMARY.

Extraction of red cinchona bark in various degrees of comminution has been studied using U. S. P. alcohol as the menstruum, and the following observations have been made.

1. It has been found that, for cinchona, in extraction by maceration, vacuum has some favorable effect for powders Nos. 10 and 20 for the initial extraction,

although on continued extraction it does not show any advantage over ordinary methods. Vacuum has no advantage in extraction of powders Nos. 40, 60 and 100 and actually has been found, during the initial extraction, to be less favorable.

2. It has been found that, for cinchona, prolonged shaking offers some advantage in all powders by ordinary maceration methods, but under vacuum it does not show any merit with coarse powders Nos. 10 and 20.

3. It has been found that, for cinchona, upon continuous extraction in a Soxhlet apparatus, No. 60 powder is too fine for such extraction while No. 40 powder gives the best results. Powders Nos. 10 and 20 do not show favorable results, apparently being too coarse for exhaustive extraction.

4. It has been found that, for cinchona, in maceration experiments, No. 60 powder is of the optimum degree of fineness on a basis of the rate of extraction, the extraction in the first hour being practically as complete as that after 144 hours. With a longer period of maceration, the extraction of No. 40 powder gradually becomes nearly as complete as that of No. 60 and since the No. 60 powder is too fine for percolation, the No. 40 can be used with advantage for such purposes. Nos. 10 and 20 powders show only a partial increase in the rate of extraction and are too coarse for practical purposes. Furthermore, these extraction studies seem to show that there is an equilibrium stage of saturation after which the extraction becomes practically stationary.

5. It has been found that, for cinchona, the use of menstruum in divided portions is more effective for extraction than a single maceration with a large quantity of menstruum.

6. It has been found that, for cinchona, the usual type of ordinary percolator is, for practical purposes, as effective as the narrow tube often used to provide a longer column of drug. In tubes where the menstruum passes as slowly as about one drop per minute through a column of powder more than 40 inches high, in contrast to the usual percolator with a column about 3 inches high, and at a rate of about 25 drops per minute, there is no appreciable difference in the final total extraction. Using a narrow tube, there is a slightly better extraction obtained in the first few fractions, but this advantage is not maintained throughout, the final sum total being about the same in each instance.

The alkaloidal and total extractive content of the various percolate fractions show that the total extractive material is removed more readily than are the alkaloids, the difference, however, not being very great.

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VISITORS AT AMERICAN INSTITUTE OF PHARMACY.

During the month of June the following visited the American Institute of Pharmacy: J. S. Davis, New Orleans, La.; P. G. Brigandi, Washington, D. C.; Miss Daisy Coty, St. Anne, Ill.; Miss Margaret Cregan, Chicago, Ill.; Stewart T. McGee, Piedmont, Calif.; Murray W. Miller, Houston, Texas; J. L. Savage, Charlottesville, Va.; E. K. Weinstein, Roxbury, Mass.; Miss Edna Zimmerman, Fergns Falls, Minn.

THE EFFECT OF PARA-SUBSTITUENTS ON THE BACTERIOSTATIC PROPERTIES OF PHENYLACETIC ACID.*

BY W. A. BITTENBENDER[1] AND ED. F. DEGERING.[1]

Many organic acids are known which possess some bacteriostatic and bactericidal action. Various investigators have attempted to correlate the structure and physical properties of these acids with this action. Alkyl substituents have been most widely investigated, particularly by Dohme, Cox and Miller (1, 2) and Coulthard, Marshall and Pyman (7) who found that as the length of the alkyl chain was increased, a peak was reached against *Eberthella typhi* but that solubility appeared to be the limiting factor against *Staphylococcus aureus*. Klarmann (17) and Suter (20), (27) studied the effect of alkoxy substituents. Browning (5) considered the effect of amino and substituted amino groups in the acridine dyes. A correlation between bactericidal power and oil-water distribution was found by Daniels and Lyons (9) in their study of an homologous series of acids. Baldinger and Nieuwland (2) found a correlation between the bactericidal action and the physical properties of the alpha-phenylalkanoic acids. The entire series of phenylalkanoic acids up to delta-phenylvaleric acid was investigated by Degering and Goshorn (14), who showed a distinct correlation between oil-water distribution, charcoal adsorption and the bactericidal action of this series of acids. Degering and Goshorn also found that these compounds were most effective over a p_H range of four to five.

Cheeseworth and Cooper (6) as well as others found that substituents in the para position were more effective than in the ortho or meta positions. Up to the present time few studies have been made of various substituents in one position of the same molecule. Such an investigation was made, however, by Labes and Jansen (19) on para derivatives of benzoic acid.

It was the purpose of this work to study the effect of para-substituents on the bacteriostatic action of phenylacetic acid and to investigate the relation of oil-water distribution to bacteriostatic properties.

EXPERIMENTAL.

A number of para-substituted derivatives of phenylacetic acid were prepared according to methods found in the literature.

Phenylacetic acid was prepared by hydrolysis of benzyl cyanide (1), conversion to the sodium salt, and purification before isolation as the free acid.

The nitro compound, *p*-nitrophenylacetic acid, was prepared by nitration of benzyl cyanide followed by hydrolysis to the acid (23). Reduction of *p*-nitrophenylacetic acid to *p*-aminophenylacetic acid was carried out by treatment with hydrogen sulfide in an ammoniacal solution of the acid (23).

Substituted amino compounds were prepared by acylation with the corresponding acyl halide. The acetyl compound, *N*-acetyl-*p*-aminophenylacetic acid, was prepared (13) by acylation of *p*-aminobenzyl cyanide and subsequent hydrolysis. Equally good results were obtained by direct acylation of *p*-aminophenylacetic acid. Orton's method (21) was used in the preparation of *N*-benzoyl-*p*-aminophenylacetic acid and the method of Jacobs and Heidelberger (15) was used to prepare *N*-chloroacetyl-*p*-aminophenylacetic acid.

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p-Hydroxyphenylacetic acid was prepared (18) by diazotization and hydrolysis of *p*-aminophenylacetic acid. This was then converted to the alkoxy derivatives, *p*-methoxyphenylacetic acid and *p*-ethoxyphenylacetic acid, by treatment with the corresponding alkyl sulfates in alkaline solution (8).

The halogen substituted derivatives, *p*-bromophenylacetic acid and *p*-iodophenylacetic acid, were prepared from phenylacetic acid by the action of the appropriate halogen and nitric acid in glacial acetic acid (10). *p*-Chlorophenylacetic acid was prepared by diazotization of *p*-aminophenylacetic acid (22), followed by a Sandmeyer reaction (24). The copper was removed by precipitation with hydrogen sulfide, the acid extracted with ether, and the product recrystallized from water.

The alkyl derivative, *p*-ethylphenylacetic acid, was prepared by (4) condensing ethylbenzene with trioxymethylene (paraformaldehyde) and moist hydrogen chloride in the presence of anhydrous zinc chloride (3), (26). The chloride was then converted to the nitrile by the reaction of potassium cyanide with an alcoholic solution of *p*-ethylbenzyl chloride. This nitrile was hydrolyzed by dilute sulfuric acid to *p*-ethylphenylacetic acid.

PREPARATION OF SOLUTIONS.

Solutions for the bacteriostatic tests were prepared and adjusted to a p_H of five. Due to lower solubility, samples of *p*-bromophenylacetic acid and *p*-iodophenylacetic acid were prepared in a concentration of one Gm. in one L. of solution. The *N*-benzoyl-*p*-aminophenylacetic acid was prepared in a concentration of 0.5 Gm. in one L. of 10% ethylene glycol. Samples of the other acids were prepared in a concentration of two Gm. in one L. of solution.

The proper amount of acid was weighed, transferred to a 100-ml. volumetric flask, and dissolved in 80–90 ml. of distilled water. The p_H of these solutions was then adjusted by addition of the necessary amount of 0.12 normal sodium hydroxide or 0.12 normal hydrochloric acid. A "universal" potentiometer assembly with a glass electrode was used in measuring the hydrogen-ion concentration. The electrode was checked against a buffer solution of known hydrogen-ion concentration before and after each period of use.

After adjustment, the solution was again poured into the volumetric flask and diluted to the mark with distilled water which had also been adjusted to a p_H of 5.0 ± 0.1. The p_H of this solution was re-checked with the glass electrode, a drop or two of alkali or acid being added if necessary, and the solution returned to the flask and stoppered.

BACTERIOSTATIC TESTS.

Escherichia coli and *Staphylococcus aureus* were used as test organisms. One ml. of the sample solution which had been made up to a given dilution with sterile distilled water of the same p_H was added to nine ml. of sterile nutrient broth which was also adjusted to a p_H of 5, thereby diluting the original concentration of the acid tenfold. The tubes of acidified nutrient broth were then inoculated with a standard loopful of a twenty-four-hour culture of *Staphylococcus aureus* or *Escherichia coli*. The tubes were incubated at 37° C. for forty-eight hours and read at the end of this period. Controls of inoculated nutrient broth were run for each bacterium tested.

All of the bacteriostatic tests were made at a p_H of five in order to minimize variations caused by the hydrogen-ion concentration of the medium. Degering, Tetrault and Goshorn (11) have shown that the small concentration of sodium and chloride ions present in the test solutions due to adjustment of the p_H is ineffective. Thus it is apparent that the results are not complicated by extraneous factors. The effect noted in each case is therefore a result due only to the presence of the test compound. By comparing a substituted compound with the parent acid, the relative effect of the substituent group may be determined. The results of these tests are presented in Table I.

DETERMINATION OF THE OIL-WATER DISTRIBUTION COEFFICIENTS.

The oil-water distribution coefficients were determined using U. S. P. cotton seed oil and one two-hundredth normal solutions of the acids. Equal volumes of oil and the acid solution were mixed in a rotatory agitator for eighteen hours at room temperature. After standing about an hour, centrifugation was employed to complete the separation.

Samples of the aqueous layer were then pipetted out and titrated by one-hundredth normal sodium hydroxide solution which was standardized against the original acid solution, phenolphthalein being used as the indicator. From the results of the known normality of the original aqueous solutions, the oil-water distribution coefficient was calculated. The results are given in Table I.

TABLE I.—BACTERIOSTATIC TESTS.

Name of Compound.	Highest Dilution Negative Growth. *Staph. Aureus.*	*Esch. Coli.*	Lowest Dilution Positive Growth. *Staph. Aureus.*	*Esch. Coli.*	Oil-Water Distribution Coefficient.
p-Bromophenylacetic acid	1/5,000	*	1/6,000	1/1,220	73.1
p-Iodophenylacetic acid	1/4,000	*	1/5,000	1/1,220	42.9
p-Chlorophenylacetic acid	1/3,000	1/1,000	1/4,000	1/1,500	23.7
N-Chloroacetyl-*p*-aminophenylacetic acid	1/3,000	1/3,000	1/4,000	1/4,000	0.25
p-Ethylphenylacetic acid	1/2,500	1/1,000	1/3,000	1/1,500	36.1
p-Nitrophenylacetic acid	1/2,000	1/610	1/2,500	1/720	2.71
p-Aminophenylacetic acid	1/1,500	1/2,000	1/2,000	1/2,500	0.13
Phenylacetic acid	1/1,000	1/1,500	1/1,500	1/2,000	1.85
p-Methoxyphenylacetic acid	1/1,000	1/1,500	1/1,000	1/1,500	2.79
p-Ethoxyphenylacetic acid	1/1,000	*	1/1,500	1/610	8.28
p-Hydroxyphenylacetic acid	*	*	1/610	1/610	0.09
N-Acetyl-*p*-aminophenylacetic acid	*	*	1/610	1/610	0.28
N-Benzoyl-*p*-aminophenylacetic acid (solution in 10% ethylene glycol)	*	*	1/610	1/610	...

* The lowest dilution gave positive growth. No killing action was observed in the dilutions possible.

CONCLUSIONS.

Interpretation of Bacteriostatic Tests.—The results of the bacteriostatic tests are shown for *Staphylococcus aureus* and *Escherichia coli* in Table I. There appears to be some variance between the two types of bacteria. The differences can usually be attributed to the varying resistance and composition of the species of bacteria.

No apparent explanation has been found for the fact that *p*-bromophenylacetic acid gives a higher maximum effective dilution than the corresponding iodo compound. This behavior is anomalous on the basis of the work of others. An explanation may be that the competing effects of decreasing solubility and increasing bacteriostatic action show a maximum for the bromo derivative, while the peak is not quite reached for the chloro compound and has been passed for the iodo compound. Another possible explanation is the "quasi-specific" activity noted by Klarmann and co-workers (17).

Moore, Day and Suter (20) found that 4-bromo-6-*n*-butylresorcinol was more effective toward *Staphylococcus aureus* than toward *Eberthella typhi*. A similar effect is noted in this research in that all three of the halogen compounds showed a greater effect with *Staphylococcus aureus* than with *Escherichia coli*.

A striking contrast results from a comparison of the data on *N*-acetyl-*p*-aminophenylacetic acid and *N*-chloroacetyl-*p*-aminophenylacetic acid. The substitution of one chlorine atom on the terminal carbon atom evidently has a very pronounced effect. No explanation of this has been offered other than the normal effect of halogen substitution. The general behavior of amino substituents

closely follows that noted by Browning and others (6) in their study of the bacteriostatic action of the acridine dyes against *Staphylococcus aureus* and *Escherichia coli*. The amino group by itself in *p*-aminophenylacetic acid increases the effective dilution over that of the free acid. When one of the amino hydrogen atoms is substituted by an acetyl group, a marked lowering in the bacteriostatic action is noted. This same lowering occurs when the amino group is replaced by a hydroxyl group as shown by the relative ineffectiveness of *p*-hydroxyphenylacetic acid.

The low effectiveness of *N*-benzoyl-*p*-aminophenylacetic acid may be attributed to the fact that it also is an acylated amino compound, and to decreased solubility caused by the large benzoyl radical. This is not in accord with the conclusion of Johnson and Lane (16) who found that the increase in bactericidal properties is a function of the size of the group introduced, since *N*-benzoyl-*p*-aminophenylacetic acid contained the largest substituent group of the compounds tested.

The results obtained from the tests on the two alkoxy compounds do not check with those of other investigators. Klarmann and others (17) found an increase in the effectiveness of alkoxy compounds with an increase in the number of carbon atoms when the tests were made on *Staphylococcus aureus*. Methoxy- and ethoxy-phenylacetic acids against *Staphylococcus aureus* gave the same maximum effective dilutions. Against *Escherichia coli*, *p*-methoxyphenylacetic acid was more effective than *p*-ethoxyphenylacetic acid. Klarmann found an increase in activity with an increase in the length of the alkoxy chain when he compared the action of his compounds against *Eberthella typhi*.

The alkyl compound gave satisfactory results, based on the comparison of aliphatic chain substituents investigated by numerous workers. The nitro group seems to increase the effectiveness against *Staphylococcus aureus* but to be of little value against *Escherichia coli*.

In their study of the substituted benzoic acids, Labes and Jansen (19) arranged their substituent groups in the following decreasing order: iodo, bromo, chloro, nitro, methyl and hydroxy. The same groups in the phenylacetic acid series, according to this study, take the order: bromo, iodo, chloro, ethyl, nitro and hydroxy.

The introduction of the methoxy group does not seem to inhibit nor enhance the bacteriostatic action of phenylacetic acid since the results against both *Staphylococcus aureus* and *Escherichia coli* were the same for each compound.

Both the bacteriostatic tests and the oil-water distribution coefficient for phenylacetic acid check with those obtained by Degering and Goshorn (14) for the same compound.

Interpretation of Oil-Water Distribution Coefficients.—The results of the oil-water distribution tests are shown in Table I. These coefficients do not coincide, in many instances, with the results from the bacteriostatic tests, but this is not an indication that there is no relationship between the two. However, it is an indication that correlation is best shown by members of an homologous series. The halogen derivatives bear this out in that the results check for the two tests. The alkoxy compounds show an increase in the distribution coefficient with an increasing number of carbon atoms in contrast to their behavior as bacteriostats.

The amino and substituted amino groups gave particularly anomalous oil-water distribution coefficients as compared with their bacteriostatic action. For instance, *p*-amino-phenylacetic acid was the lowest and *N*-acetyl-*p*-aminophenyl-acetic acid the highest even though the highest maximum effective dilution was given by *N*-chloroacetyl-*p*-aminophenylacetic acid.

If the phenylacetic acid molecule is considered as a constant and the solubility class of the compounds predicted on the basis of the tables of Shriner and Fuson (25), a very interesting result is obtained. The bromo, iodo, ethyl and chloro substituent groups fall in Class I, the ethoxy and methoxy groups are border-line cases between Class N_2 and N_1, the nitro, *N*-acetylamino and *N*-chloroacetylamino groups fall in Class M, the amino group falls in Class B, and the hydroxy group falls in Class A_2. The groups arranged in the order of decreasing oil-water distribution coefficients are found also to be in the order of their increasing solubilities in water. Although the assumption made in predicting these solubilities may seem erroneous, the result is entirely in accord with the relationship between oil-water distribution and solubility.

SUMMARY.

1. Twelve para-substituted derivatives of phenylacetic acid have been prepared, and bacteriostatic tests made against *Staphylococcus aureus* and *Escherichia coli*.

2. Oil-water distribution coefficients have been determined and their relationship to bacteriostatic activity has been discussed.

3. The para-bromo derivative was the most effective of those studied.

4. Substitution of a chlorine atom on the acetyl group of *N*-acetyl-*p*-amino-phenylacetic acid caused a very marked increase in bacteriostatic action.

5. The substitution of hydroxy and *N*-acetylamino groups decreased bacteriostatic action, while all other substituents studied enhanced it by varying amounts.

6. Both alkoxy derivatives gave the same maximum effective dilution against *Staphylococcus aureus*, but *p*-methoxyphenylacetic acid was more effective than *p*-ethoxyphenylacetic acid against *Escherichia coli*.

7. *N*-Chloroacetyl-*p*-aminophenylacetic acid, *p*-aminophenylacetic acid, *p*-methoxyphenylacetic acid and phenylacetic acid were found to be more effective against *Escherichia coli* than against *Staphylococcus aureus*.

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INVESTIGATIONS ON THE CHEMISTRY AND PHYSIOLOGY OF THE VENOM OF THE HONEY BEE (*APIS MELLIFICA*).*

BY W. M. LAUTER AND O. J. GRIGGS.

The recent investigations of Hahn and collaborators (1, 2, 3, 4), Reinert (5) and Essex, Markowitz and Mann (6) have thrown considerable light upon the chemical and physiological properties of bee-venom. The earlier work by Flury (7), Langer (8) and Phisalix (9) described methods of obtaining the venom which soon were shown to be less efficient than those adopted by later investigators. Beck (10) gives a description of obtaining the venom for laboratory purposes which appears to be best suited to obtain as little contaminated a venom solution as is possible.

The venom is produced by the insect in the so-called poison-sac by mixing the secretions of three glands. Two of these are known as the acid glands while the third one is called the alkaline gland, because of the p_H of their secretions. Carlet's (11) experiments seemed to show that only the mixture of the two liquids has the typical toxic properties of bee-venom. Hesselhaus (12) believes that the acid glands alone furnish the toxin, and that the secretion of the alkaline gland serves to neutralize the acid that remains in the sting.

Recent investigations, however, seem to indicate that the venom is secreted only in one gland. This gland is in the average 14 mm. long and has a diameter of 0.19 mm. The gland is forked at its end, and this division into two parts has been the reason for earlier investigators to arrive at the conclusion that two different glands are present. The so-called third venom gland which enters just below the poison-sac seems to be merely a producer of a lubricating substance and does not contribute at all to the venom itself.

Most of the work, although this is not especially mentioned, has obviously been done on the northern European variety of bees, the so-called British Black (*Apis Mellifica Mellifica*), an insect which differs somewhat in color and other characteristics from the so-called Italian race of bees (*Apis Mellifica Ligustica*), which is practically the only variety obtainable in the

* From the Research Department R. J. Strasenburgh Company.

United States. We have obtained our venom entirely from summer bees of the Italian variety. In general, Beck's method was used, and the venom was obtained in a fairly pure form.

We allowed bees to sting into an animal membrane which had been stretched over a small glass vessel containing a sterile solution of 0.9% NaCl solution. Each animal is caught with a pair of pincers and brought in contact with the wet membrane. The animal will sting at once; the drop (about 0.35–0.50 mgms.) of venom liquid dissolves in the liquid, and the sting remains in the membrane. The material is filtered and the small residue extracted once more with hot 0.9% NaCl solution. We used 2000 bees for each experiment. The solutions were then evaporated *in vacuo* to a volume of 20 cc. and slowly poured into 400 cc. acetone. This same method had been employed successfully by K. A. Forster[1] and also by Hahn and Ostermayer (1). The precipitate was centrifuged with acetone and dried *in vacuo*. The yield from 2000 bees was 220 mg. dried acetone precipitate.

The analyses from 6 such lots were as follows:

C—43.9–44.5%
H— 7.4– 7.6%
N—15.4–14.4%
S— 1.1%
P— 0.48%
Mg— 0.1%

This coincides with the results obtained by Hahn who found that the "crude venom" of their description has about 0.4% Mg. These authors maintain that other metals (Na, K, Fe, etc.) are not even present in traces.

This analysis differs from the one given by Reinert for a "purified bee-venom" through alcohol precipitation mainly in that we have found sulfur in all our acetone precipitates. In the crude liquid venom as it is secreted by the insect without further purification we found considerable amounts of sulfur, in the average 2.7%.

The phosphorous content when obtained by the method described above was 0.48%, but when a different method of extracting the venom from the insects was used, a far larger percentage was obtained when the stings left on the upper side of the membrane were ground, weighed and extracted twice with $^1/_2N$ Formic Acid solution, the average phosphorous content was 2.9%. This amount varied very little.

The specific gravity of the crude venom is 1.1313, it is a clear liquid, reacts acid, tastes bitter and has a faint aromatic odor. When dried at room temperature a residue of about 30% is obtained.

Beck was the first to point out that the principal toxic actions of bee-venom might be due to a proteosis. This has been experimentally proven by Hahn and Reinert. Investigations to be published later which we undertook also showed this to be the fact. In conformity with Klopstock and Neter (13), we found that the bee-venom might contain saponins, because small amounts of tannin destroyed the hemolytic action in the same manner as is the case with the saponins. Flury suggested that the saponin-like component of bee-venom might be a link between the albumen-free sapotoxins of animal origin like Crotalotoxin and Ophiotoxin of snake venoms and the toxins of the cantharides group.

SUMMARY.

A physiologically active bee-venom "solid concentrate" obtained by acetone precipitation was analyzed. It contained sulfur.

The minimum lethal dose for intravenous injections into the white mouse was 3.5 Gm. per Kg. bodyweight.

Twenty-two γ solid acetone precipitate hemolize 0.1 cc. rabbit blood erythrocyte suspension. (1–453,000 dilution.)

Twenty γ in physiological salt solution show definite necrotic action when injected intracutaneously.

[1] Private communication from K. A. Forster.

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QUANTITATIVE ESTIMATION OF THE POTENCY OF DIGITALIS BY THE CAT METHOD IN RELATION TO SECULAR VARIATION.*

BY C. I. BLISS[1] AND J. C. HANSON.

Determinations of the acute toxic dose of a drug or poison follow one of two experimental procedures. The first and more common method is to administer different, predetermined dosages to successive groups of animals, so that each individual in a group receives the same dose. The percentage mortality from a given dose is the measure of effect and from a series of such dosages and percentages the dosage-mortality curve and the median lethal dose can be computed. These same values are obtained directly in the second, more specialized procedure, in that the lethal dose is determined separately for every individual. An example is the cat unit for cardiac glucosides, where the drug is infused into the venous system so slowly that the latent period between infusion and cardiac failure is presumably negligible in comparison with the total time of injection. The results, however, are sometimes computed so as to obscure the similarities between the two procedures. Moreover, there are seldom safeguards for secular fluctuations in susceptibility which are known to complicate many comparisons of the LD50 based upon the first method. Such safeguards have been observed for several years in tests of "Digiglusin" (Digitalis Glucosides, Lilly) by the cat method at the Lilly Research Laboratories, and it is of interest to examine the bearing of these results upon the so-called "cat unit" for cardiac glucosides and related drugs.

EXPERIMENTAL PROCEDURE.

The experimental procedure followed the general method first described by Hatcher and Brody (9). Digitalis extract was infused into the femoral vein of the etherized cat at the rate of 1 cc. per minute until the heart stopped. An assay required eight cats, all from the same source, four on the "Digiglusin" Standard and four on a new sample of extract which had been evaluated previously by the one-hour frog method as described in the U. S. Pharmacopœia. In conducting a test, four cats were etherized and prepared on four animal boards for the infusion of one of the two preparations in dilutions of 1:33½, the entire process requiring from 10 to 20 minutes. When

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all were ready, infusion was started in all four cats within a minute or two of each other. The four animals tested in parallel were exposed equally, therefore, to environmental influences.

From the data accumulated in the course of these tests, 52 series have been selected for statistical analysis. Since all of these were recorded by the junior author, any differences between series cannot be attributed to observer's bias. The analysis has been further restricted to the group in each series infused with the laboratory standard of "Digiglusin," which is kept in a refrigerator at 40° F. and checked for potency every three months, so that all solutions had presumably the same potency. The 52 assays covered a 19-month period from January 1937 to July 1938, inclusive, and were spaced at irregular intervals through this period. Animals for testing were not selected as to sex and of the 208 cats, 130 were males and 78 were females. They varied in weight from 1.7 to 3.5 Kg. and averaged 2.5 Kg. At a constant infusion rate of 1 cc. per minute, the infusion period varied from 38 to 144 minutes with a mean (geometric) of 72 minutes. The weight of each cat and its individual lethal dose in cc. (×0.1) have been transformed to logarithms and are given in full in Table I. These represent the record upon which the computations are based.

Comparison of the Variation between Series with That within Series.—The presence or absence of a secular variation in the individual lethal dose of digitalis for cats can be tested by comparing the variation between assays with that within assays. A significantly larger average difference between groups of four cats than between the individuals comprising these groups would show that secular changes were present. Such a comparison can be made readily by the analysis of variance, a procedure that is especially suitable when the units in the computation follow the normal curve of error. Many authors have shown that although the distribution of the individual lethal dose is commonly skewed, the logarithm of the dose is usually distributed symmetrically and normally. For this reason the original records in Table I have been transformed to logarithms as a preliminary stage in the analysis.

TABLE I.—BASIC RECORD ON EACH INDIVIDUAL CAT IN 52 ASSAYS WITH STANDARD "DIGIGLUSIN," SHOWING THE LOGARITHMS OF THE BODY WEIGHT IN KG. AND OF THE DOSE PER CAT IN 10 CC. UNITS OF EXTRACT.

Asay Number.	Date.	Logarithm of Body Weight in Cat Number. 1.	2.	3.	4.	Logarithm of Dose in Cat Number. 1.	2.	3.	4.
1	1/13/37	0.388	0.382*	0.323*	0.379	0.919	0.900	0.699	0.905
2	1/26/37	0.394*	0.498	0.406	0.414	0.866	0.910	0.871	0.712
3	1/27/37	0.341*	0.378	0.323*	0.416*	0.736	0.708	0.735	0.816
4	2/ 2/37	0.415*	0.370	0.458*	0.399*	0.841	0.808	0.932	0.827
5	2/ 4/37	0.378*	0.362*	0.369*	0.339*	0.906	0.769	0.778	0.736
6	2/23/37	0.454	0.365*	0.443*	0.351*	0.944	0.946	0.949	0.949
7	2/26/37	0.447	0.370*	0.427	0.463*	0.782	0.695	0.921	0.821
8	3/ 1/37	0.465*	0.463	0.500	0.514	0.982	0.975	0.962	0.948
9	3/ 4/37	0.474	0.380	0.359*	0.391	0.834	0.752	0.861	0.888
10	3/ 5/37	0.479*	0.472	0.403	0.487	0.853	1.000	1.003	0.997
11	3/25/37	0.346	0.332	0.448	0.473	0.927	0.739	0.967	0.970
12	4/ 6/37	0.459*	0.350*	0.332*	0.498	0.799	0.658	0.672	0.845
13	4/19/37	0.418	0.456	0.328	0.521	0.795	0.763	0.776	0.938
14	4/26/37	0.401*	0.334	0.515*	0.424	0.963	0.794	0.981	0.856
15	5/ 7/37	0.536	0.483	0.518	0.501	1.002	0.946	1.076	1.047
16	5/18/37	0.384*	0.383*	0.459	0.323*	0.918	0.867	1.023	0.625
17	6/ 2/37	0.379	0.401	0.380	0.384	0.769	0.762	0.710	0.768
18	6/ 8/37	0.329*	0.354	0.447	0.366	0.893	0.823	0.892	0.750
19	6/17/37	0.480	0.390	0.431	0.383*	0.904	0.823	0.849	0.818
20	6/22/37	0.437	0.486	0.325	0.399*	0.916	0.924	0.712	0.967
21	10/26/37	0.425	0.365*	0.379*	0.313*	0.897	0.670	0.699	0.793
22	10/26/37	0.324*	0.301*	0.325	0.355*	0.704	0.828	0.775	0.647
23	1/19/38	0.337*	0.328*	0.399	0.412	0.777	0.782	0.760	0.865
24	2/ 1/38	0.348*	0.361*	0.359*	0.418	0.804	0.838	0.835	0.883
25	2/ 2/38	0.399*	0.468*	0.326*	0.418*	0.901	0.947	0.857	0.990

TABLE I.—BASIC RECORD ON EACH INDIVIDUAL CAT IN 52 ASSAYS WITH STANDARD "DIGIGLUSIN," SHOWING THE LOGARITHMS OF THE BODY WEIGHT IN KG. AND OF THE DOSE PER CAT IN 10 CC. UNITS OF EXTRACT. (*Continued from page 522.*)

Assay Number.	Date.	Logarithm of Body Weight in Cat Number. 1.	2.	3.	4.	Logarithm of Dose in Cat Number. 1.	2.	3.	4.
26	2/ 3/38	0.331	0.431*	0.404*	0.451	0.879	0.983	0.862	0.965
27	2/15/38	0.365*	0.280*	0.354	0.315*	0.825	0.707	0.693	0.679
28	2/18/38	0.470	0.413	0.445	0.316	0.974	0.968	0.906	0.772
29	2/22/38	0.348	0.375*	0.374*	0.304*	0.814	0.939	0.957	0.817
30	2/28/38	0.342*	0.406*	0.336*	0.318*	0.816	0.831	0.799	0.932
31	3/16/38	0.505	0.334	0.515	0.488	0.848	0.699	0.939	0.938
32	3/22/38	0.393	0.387	0.461	0.414	1.009	0.867	0.901	0.782
33	3/29/38	0.416	0.387	0.416	0.369	0.971	0.891	0.980	0.841
34	4/ 4/38	0.414	0.337*	0.367	0.454	0.877	0.829	0.889	1.036
35	4/ 5/38	0.228	0.247	0.343	0.430	0.737	0.659	0.821	0.949
36	4/19/38	0.434	0.442	0.243	0.331	0.950	0.908	0.785	0.875
37	4/22/38	0.355	0.344	0.502	0.492	0.821	0.813	1.092	0.971
38	4/28/38	0.473	0.482	0.301	0.397*	0.941	0.904	0.843	0.780
39	4/29/38	0.281	0.454	0.280*	0.371	0.814	1.003	0.767	0.833
40	5/ 9/38	0.374	0.317	0.332	0.329	1.018	0.772	0.867	0.822
41	5/26/38	0.326	0.368	0.395	0.538	0.717	0.978	0.983	1.098
42	5/27/38	0.447	0.461	0.529	0.462	0.931	0.925	1.158	0.927
43	6/ 1/38	0.424*	0.373*	0.394	0.452	0.923	0.812	0.914	0.921
44	6/15/38	0.348*	0.450	0.529	0.545	0.839	0.769	0.909	0.958
45	6/22/38	0.360*	0.400*	0.490	0,440	0.849	0.920	0.971	0.881
46	6/23/38	0.446	0.360*	0.318	0.333	0.946	0.822	0.758	0.818
47	6/28/38	0.350	0.367*	0.497	0.417	0.743	0.792	0.853	0.799
48	6/29/38	0.461	0.269*	0.475	0.246*	0.962	0.707	0.958	0.699
49	7/ 5/38	0.395	0.427	0.383	0.292*	0.886	0.880	0.912	0.653
50	7/ 7/38	0.333*	0.334	0.313*	0.376	0.738	0.580	0.828	0.915
51	7/12/38	0.411	0.446	0.318*	0.332*	0.826	0.973	0.699	0.838
52	7/15/38	0.504	0.258*	0.361	0.472*	0.952	0.677	0.713	1.009

* Indicates females, those without are males.

Dosages are ordinarily expressed in mg. of drug per Kg. of body weight, although it is usually specified that the experimental animals should not exceed certain weight limits. This specification alone shows that the practice of dividing the dose per animal by its weight is essentially a convenient approximation. Ideally, every cat should be of exactly the same size, so that no correction for body weight would be necessary, but this, of course, was not the case. Not only did the four cats comprising any one group vary in size, but the average weight of different groups varied almost as much, from 2.1 to 3.2 Kg. An apparent variation in susceptibility might be attributed to differences in body mass unless it were shown that the usual dosage ratio corrected these differences satisfactorily in this particular series of tests. The difficulty has been solved by the analysis of covariance, using the logarithm of the dose per cat as the criterion of digitalis effect and the logarithm of body weight as a concomitant measure to be equalized in the calculation. By this procedure the variation in weight was corrected on the basis of the best-fitting straight line relating log-dose and log-weight *within* groups of cats that were tested simultaneously.

The mode of computation has been described in detail by R. A. Fisher (6), so that it need only be summarized here in presenting the results. All determinations of the lethal dose per individual cat (in logarithms) may be considered as independent estimates of one value which is represented best by the mean log-dose, 0.8577. The variation about this mean, measured by the total sum of the squared deviations, includes two components, that due to the differences between the 52 group means and the general mean and the reminder due to departures of the four individual records in each assay from its own group mean. The sums of the squares of these differences are listed in the Column Y^2 of Table II and equivalent values for the body weights, W^2,

and the product WY are given in the two preceding columns. From WY and W^2 within assays the slope of the straight line relating log-dose to log-weight has been computed as $b = \frac{WY}{W^2} = 1.085$, which was then used to correct the variation in the log-dose (Y^2) for inequalities in body weight. When the corrected or "reduced" sum of Y^2, 0.6535, was divided by the reduced degrees of freedom,

TABLE II.

Analysis of Data in Table I by Covariance, where W is the Logarithm of the Body Weight and Y is the Logarithm of the Dose Per Cat, Both in Terms of Deviations from Their Respective General Means.

Variation.	Degrees of Freedom.	Sums of W^2.	Sums of WY.	Sums of Y^2.	Regression Coefficient. b.	Reduced Sum of Y^2.	Reduced Mean. Y^2.
Between assays	51	0.35140	0.35319	0.88491	.....	0.53130	0.010418
Within assays	156	0.56657	0.61496	1.32092	1.08540	0.65345	0.004216
Total	207	0.91797	0.96815	2.20583	1.05466	1.18475	.....

155, the quotient, 0.004216, measured the net variance for the individual dose in logarithms exclusive of differences between days. The corresponding term for the variance between successive assays or groups of four cats was 0.010418 or more than twice as large. To find whether the variation between assays was significantly larger than that within assays, the variance ratio, "F" in Snedecor's terminology (11), was computed from the two corrected variances as $\frac{0.010418}{0.004216} = 2.471$. By reference to a table giving the expected values of the variance ratio at $P = .001$ (7), the observed ratio was clearly larger than that which would be exected at $n_1 = 51$ and $n_2 = 155$, so that there is less than 1 chance in 1000 that the cats in this series did not vary in susceptibility from one assay to another to a greater extent than from one individual to another on the same day. There can be no doubt, therefore, that under these experimental conditions digitalis can be assayed with greater precision if the sample is always compared with the standard on the same day by means of cats from the same source.

In correcting the lethal dose per cat for variations in body weight, no arbitrary assumptions have been made as to the exact relation between the two factors. It is of interest, therefore, to test how nearly the correction computed from the data agrees with the conventional dosage ratio which it replaced. If computed by means of logarithms, the logarithm of the dosage ratio for an individual cat in mg. per Kg. would be $Y - W$. The equation used in the foregoing calculation was $Y - bW$, with b equal to 1.085 instead of 1 as is usually assumed. The regression coefficient b is equivalent in the size factor as defined by Bliss (1) to the exponent h in the expression $\frac{\text{mg.}}{(\text{K}_\text{g.})^h}$ when both drug or poison and body mass are expressed in original weight units. Several instances have been reported (4) in which h does not equal 1. In the present case, however, $h = 1.085 \pm 0.086$ which is not significantly greater than 1, so that the conventional dosage ratio would be justified here and its logarithm should lead to substantially the same results as have been obtained by covariance.

Nature of the Variation between Assays.—The above analysis demonstrates that the susceptibility of cats to digitalis varied significantly between assays. Was this secular change seasonal or fortuitous? In order to correct for variations in body weight, the logarithm of the individual lethal dosage ratio ($x = y - w$) has been computed for all of the cats in Table I. From these the mean log-ratio ($\bar{x}_p$) was determined for each of the 52 assays and plotted in Fig. 1 against the date of the test. It is evident from inspection that there was no consistent or marked seasonal trend over the two years, which is in agreement with the experience of previous workers (12). With the possible exception of the last few months of the experiment, the group means seemed to fall quite fortuitously above and below the general mean ($\bar{x}$), indicated by the horizontal broken line. If the variation were really random, the distribution of the means for individual assays should approach the normal curve of error. This has been tested by computing two constants which in the normal curve are equal to zero, that for skewness, $g_1 = -0.461 \pm 0.330$, and that for

kurtosis, $g_2 = -0.618 \pm 0.650$. Since neither of these differed significantly from zero, the observed variation in the means might well have been random. It is clear, therefore, that the absence of seasonal trends is no guarantee against pronounced secular variations in susceptibility.

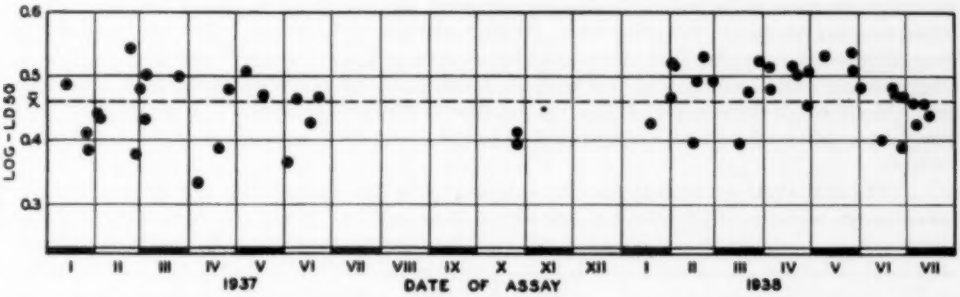

Fig. 1.—Relation between date of test and log-LD50 for digitalis in etherized cats. Each log-LD50 is the mean log-dose for four cats tested simultaneously.

In order to compare the relative magnitudes of the variation between and that within assays, the logarithmic dosage-ratios whose means are shown in Fig. 1 have been computed by the analysis of variance (Table III). As was to be expected, the two mean squares differed but little

TABLE III.

Analysis of Variance for the Logarithm of the Dosage-Ratio Computed from the Data in Table I, in Terms of the Deviations from the General Mean.

Variation.	Degrees of Freedom.	Sum of Squares.	Mean Square or Variance.	Standard Deviation.
Between assays	51	0.52992	0.010391	0.10193
Within assays	156	0.66478	0.004261	0.06528
Total	207	1.19470	....	...

from the equivalent "reduced" means obtained by covariance (Table II). The standard deviations in Table III, which are the square roots of the mean squares, show the relative magnitude of the errors affecting comparisons between groups of four cats on different days as contrasted with comparisons between cats within the same group.

These two standard deviations, however, are not direct indices to the relative importance of the two sources of variation. Although the mean square or variance within assays is independent of the differences between assays or groups, the variation between assays in Table III is compounded from both sources. Snedecor (10) and others have shown that when there are four units in each group, the mean square between groups or assays is equal to $4\,s_1^2 + s_2^2$ and that within assays to s_2^2. From Table III, $s_2^2 = 0.004261$ and $4\,s_1^2 + s_2^2 = 0.010391$ or $s_1^2 = 0.001532$. In terms of standard deviations the variation within assays, $s_2 = 0.0653$, would be augmented by the additional variation between assays, $s_1 = 0.0391$, unless comparisons between unknown and standard were restricted within four-cat groups. It is not sufficient, therefore, to test the standard digitalis extract occasionally between assays of unknown preparations as a control on the technique of a given laboratory or worker, as has been advocated (12). Tests with cats should be run in parallel, quite as is required in the frog assay.

The source of the variation between assays is to be sought in the origin of the successive batches of cats rather than in the environmental conditions of the testing laboratory which were relatively constant and hardly a major cause of variation. The cats were purchased from widely separated dealers who gathered them as needed and sometimes covered a considerable distance in filling a single order. Since they came from very heterogeneous sources, the cats in any one lot probably agreed better than cats from different lots when delivered to the laboratory. This simi-

larity extended to the susceptibility to digitalis and to body weight, which was significantly more uniform within than between assays. Once received at the laboratory the animals were used fairly promptly since cats do not thrive when confined in cages.

Relation of the Cat Unit to the Dosage-Mortality Curve.—The cat unit is usually computed as an arithmetic mean of the individual dosages, although the median lethal dose or LD50 is the preferred measure for dosage-mortality data. If the logarithm of the dosage ratio for individual cats were distributed normally, then the median lethal dose or LD50 for slow infusion of digitalis in etherized cats could be estimated best from the mean logarithm of the doses observed in any one test. Moreover, a demonstration that the log-dose is distributed normally in the present tests would give additional support to the use of logarithms in the above analyses of variance and of covariance.

The individual determinations were exposed to two unequal sources of variation, one between assays or groups of four and a second within these groups. In view of the random nature of the secular variation and the absence of any seasonal curve which could be used to correct the log-dosage-ratios of the successive groups, the ratio of the standard deviations in Table III provided the most satisfactory basis for adjusting the individual observations. A constant factor was added to each term in a group which reduced the departure of the group mean from the general mean to $\frac{0.06528}{0.10193} = 0.6404$ of the original observed difference. This corrected the individual values for secular variation so that the standard deviation based upon all 208 adjusted log-dosages was the same as that observed originally within assays. Since some of these corrections were positive and some negative, the mean log-dosage was unchanged.

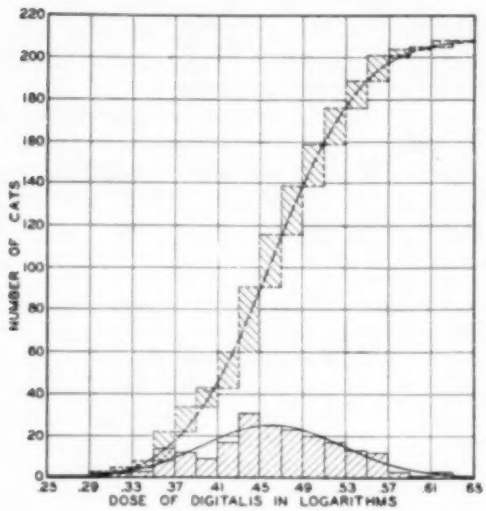

Fig. 2.—Initial and cumulative frequency distributions of individual lethal dosages in logarithms of standard "Digiglusin" in 10 cc. units per Kg. after correction for secular variation. The frequencies expected by the normal curve of error are shown by smooth curves.

The resulting distribution has been plotted as a frequency histogram along the base of Fig. 2, which shows the number of cats reacting in each dosage interval on the abscissa. The normal curve of error has been drawn over the histogram and it is apparent that the observed values agreed moderately well with expectation. The same data have been plotted in a cumulative form in the upper part of the diagram by moving each block vertically upward until its lower edge was contiguous with the upper edge of the preceding block. The normal curve in its cumulative, sigmoid form has been drawn over this block diagram as well and its similarity to the dosage-mortality curve in which percentage kill is plotted against log-dose is at once apparent.

The frequency histogram in the lower part of Fig. 2 is not unlike "Kurve 1" in van Wijngaarden's (12) paper on the digitalis assay in cats except that he plotted units of dosage rather than of log-dosage along the abscissa. This diagram has been quoted widely and seems to show that his original dosages were distributed normally. The figure, however, is a composite, covering different assays on different samples of digitalis so that the results based on more homogenous portions of this complex would be more nearly comparable to the evidence reported here. An analysis of these restricted records (based on his second and third diagrams) shows that the individual lethal dosages were not distributed symmetrically. When dosages were transformed to logarithms, this asymmetry largely disappeared, leading to the same conclusion as Fig. 2 of the present paper. His standard deviation, however, was 0.127 in contrast to the 0.0653 obtained here, so that our data were considerably more consistent than those reported by van Wijngaarden.

A number of writers have shown that the sigmoid dosage-mortality curve can be plotted as a straight line by converting dosages to logarithms and percentage mortalities to probits or their equivalent (3). The same transformation has been used in the present case, the cumulated frequencies being changed to percentages and then to probits to obtain the rectilinear diagram of Fig. 3. The observed values have been fitted by a straight line which passes through the mean log-dose of the original observations at 5 probits with a slope equal to the reciprocal of the standard deviation within assays from Table III and has the equation $Y = 5.00 + 15.32\ (X - 0.4613)$, where Y is the mortality in probits and X is the dose of digitalis in logarithms. One could conclude from the graphic analysis that the logarithm of the individual lethal dose followed the normal distribution, but for confirmation the constants for skewness and kurtosis have been determined, neither of them varying significantly from zero ($g_1 = -0.136 \pm 0.169$, $g_2 = -0.150 \pm 0.336$).

The equivalence of Fig. 3 to the rectified dosage-mortality curve gives added support to the interpretation of the dosage-mortality curve first introduced by Gaddum (8). The difference between them is merely of experimental and computational technique. When the individual lethal doses are transformed to logarithms before computing the mean, the antilogarithm of this mean logarithm (the geometric mean) is the median lethal dose or LD50. In this series of tests the log-LD50 of standard "Digiglusin" for 208 etherized cats was 0.4613 or (since the log-dosages were in 10 cc. units) LD50 = 28.93 cc. of dilute tincture per Kg. when injected at the rate of 1 cc. per minute.

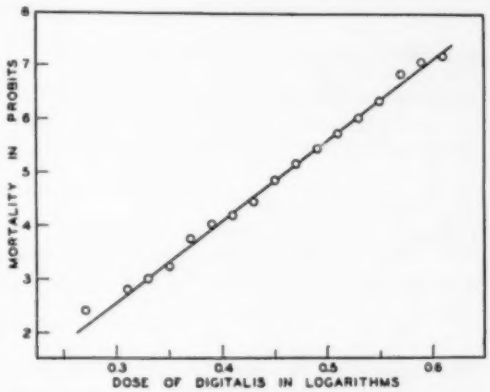

Fig. 3.—The cumulative curve of Fig. 2 after transformation from frequencies to probits.

A Modified Procedure for Cat Assays.—It is evident from the above study with a single preparation that when an unknown sample is compared with the standard within groups of four cats tested in parallel, assays will have a smaller error than when the comparison is between such groups or sets. The procedure would be to infuse in any one set two of the cats, selected at random, with the unknown preparation and the remaining two with the standard. This is repeated with additional sets each of four cats until the required precision is attained. The basic unit for analysis is the logarithm of the dosage ratio for each cat in cc. per Kg. (or in 10 cc. per Kg.), which is here designated by the symbol x. The computation both of relative potency and of its error is facilitated by the use of logarithmic units.

The log-ratio of potencies, M, is given by the equation

$$M = \frac{D}{N'} \qquad (1)$$

where D is the difference obtained by subtracting the sum of the log-doses for the unknown from the sum of the log-doses for the standard, disregarding the differences between groups of four cats or the number of groups involved, and N' is the total number of cats tested on each preparation. M gives the amount of standard required to produce the same response as one unit of unknown and can be changed to the logarithm of the percentage potency merely by adding 2. The antilogarithm of $M + 2$ is the percentage potency of the unknown sample.

In computing the standard error of M it is important to exclude any contributions from the differences between the four-cat groups since the inherent balance of the design has already excluded them from the estimate of M. The following equation for the standard error of M, s_M, has this characteristic:

$$s_M = 2\sqrt{\frac{S(x^2) - \frac{S(C^2)}{4} - \frac{D^2}{2N'}}{N'(3N' - 2)}} \qquad (2)$$

where $S(x^2)$ is the sum of the squares of the original log-dosages for all cats on both standard and unknown, C is the sum of the four log-doses in any one group on both standard and unknown, which is squared and summed for all groups in the assay ($= S(C^2)$), and the other symbols have the same significance as in Equation 1. When there are only two groups each of four animals, Equation 2 can be simplified

$$s_M = \sqrt{\frac{S(x^2) - 0.125(T^2 + D_g^2 + D^2)}{10}}, \qquad (2a)$$

where T is the total of all log-dosages and D_g is the difference between groups obtained by subtracting the sum for the four cats in the second group from the sum in the four cats in the first group, disregarding differences between unknown and standard.

The standard error, s_M, is used to answer the question: does the potency of the sample or unknown differ significantly from that of the standard? This is determined from the ratio $t = \frac{M}{s_M}$, which is then referred to a table giving the expected values of t for different levels of significance, such as that in the collection of tables by Fisher and Yates (7). If the observed t exceeds that expected by chance at odds of 1 in 20, the sample is judged to differ significantly in potency from the standard. The expected value of t depends upon the degrees of freedom (n) in the error which for any individual assay is given by the rule $n = \frac{(3N' - 2)}{2}$, where, as before, N' is the number of cats tested either with the standard or the unknown.

To determine the approximate standard error of potency in original units, a convenient rule for converting from logarithms is that given by Cochran (5) as

$$\text{s.e. of relative potency} = 2.3026\ (\text{antilog } M)s_M. \qquad (3)$$

For percentages this is multiplied by 100.

The individual log-dosages for three assays of "Digiglusin," each based upon two groups of four cats, are given in Table IV and may be used to illustrate the above calculation. From the

TABLE IV.

The Lethal Dose in Logarithms for Individual Cats in Three Bioassays of "Digiglusin" (Digitalis Glucosides, Lilly).

Assay Number.	Log. Dosage-Ratio (X) for Individual Cats in First Group. Unknown.		First Group. Standard.		Second Group. Unknown.		Second Group. Standard.		Total (T).	Differences between Groups. 1st–2nd (D_g).	Differences between Solutions: Standard –Unknown (D).
1	0.375	0.461	0.387	0.421	0.574	0.455	0.540	0.536	3.749	−0.461	0.019
2	$\bar{1}$.986	$\bar{1}$.918	0.468	0.422	0.082	$\bar{1}$.880	0.542	0.383	1.681	−0.093	0.949
3	0.665	0.473	0.644	0.455	0.443	0.350	0.535	0.493	4.058	0.416	0.196

eight log-doses (x) in each row the total (T) and the differences between groups (D_g) and that between standard and unknown (D) have been computed and listed in the last three columns of the table, N' being 4 in all cases. Substituting the results for the first assay in Equation 1, $M = \frac{0.019}{4} = 0.00475$, and in Eq. 2a, $s_M = \sqrt{\frac{1.795553 - 0.125(3.749^2 + 0.461^2 + 0.019^2)}{10}} = 0.03474$. Since M was smaller than its error, it is clear without further test that the potency of the first sample did not differ significantly from that of the standard. To convert to percentages, the antilogarithm of $2 + 0.00475 = 2.00475$ was read from a table of logarithms as 101.1 per cent, while from Equation 3 its standard error was $(2.3026)(101.1)(0.03474) = 8.10$, so that this sample or unknown showed 101.1 ± 8.1 per cent of the potency of standard "Digiglusin." A similar calculation for the second assay led to $M = 0.4872 \pm 0.0604$, from which $t = \frac{0.4872}{0.0604} = 8.07$ and $n = \frac{12 - 2}{2} = 5$. The observed t was larger than that expected at $P = 0.001$, so that there was no question that the 307 ± 43 per cent potency of the sample was in excess of the standard. Following factory dilution of 2.8

times, it gave the results in the third assay of Table IV, from which a relative potency of 111.9 ± 18.4 per cent was computed.

The standard deviation of the log-dosage for standard "Digiglusin" from the records on 208 individual cats is equivalent to the slope of the standard dosage-mortality curve in alternate techniques of bioassay, the one being the reciprocal of the other. From the slope of a standard curve one can estimate the expected precision of a given experimental procedure. The standard deviation within assays, $s = 0.06528 \pm 0.00369$, can be used similarly to compute the expected variation in the estimate of potency. Even when both standard and unknown have exactly the same potency, most assays will fall somewhat above or below the expected value of $M = O$ or 100 per cent potency. If in every group of four cats, two are tested with the standard and two with the unknown, the extent of the expected variation may be calculated from the standard deviation and a table of the statistic t. In Table V the limits are given in terms of the log-ratio of potencies, M, and in Table VI the same values after conversion to percentages. Statisticians usually require for significance that a divergence must be of sufficient magnitude that in the absence of a real difference it would not be expected to occur by chance oftener than once in 20 tests or assays. A determination of potency based upon only two groups of cats, for example, as in the assays shown in Table IV, could vary from 76 to 131 per cent and still pass the requirement for standard or 100 per cent potency.

TABLE V.

Expected Variation in the Log-Ratio of Potencies (M) when Both Standard and Sample Have the Same Potency. This Table Is Based upon a Standard Deviation of $s = 0.06528$ and May Be Used when the Observed s_M Falls within the Limits of the Last Column ($P = 0.05$).

Number of Groups in Assay.	Number of Cats on Each Solution (N').	The Observed M, Either + or −, May Reach or Pass This Level Once in 5 Assays.	10 Assays.	20 Assays.	50 Assays.	100 Assays.	Observed s_M Must Fall within Limits of.
2	4	0.068	0.093	0.119	0.155	0.186	0.009 − 0.083
3	6	0.053	0.070	0.087	0.109	0.126	0.016 − 0.060
4	8	0.044	0.059	0.072	0.089	0.101	0.017 − 0.048
5	10	0.039	0.051	0.063	0.077	0.087	0.017 − 0.041
6	12	0.036	0.046	0.056	0.068	0.077	0.017 − 0.037

Tables V and VI can be used to segregate the samples that differ in potency from the standard in excess of the narrower limits of 85 and 118 per cent with a minimum expenditure in the retesting of chance variants. For routine tests, two sets totaling eight cats would be used and all samples for which the log-ratio of potencies M does not exceed ± 0.068 passed as having standard potency in agreement with the frog assay. Samples differing by more than this would be held for further testing. If the combined result with one additional set of four agrees within $M = \pm 0.070$,

TABLE VI.

Expected Variation in the Observed Percentage Potency of the Unknown when Both Standard and Unknown Have the Same Potency.

Number of Groups in Assay.	Total Number of Cats.	The Observed Percentage Potency of the Unknown May Reach or Pass These Limits Once in 5 Assays.	10 Assays.	20 Assays.	50 Assays.	100 Assays.
2	8	85–117	81–124	76–131	70–143	65–154
3	12	89–113	85–118	82–122	78–129	75–134
4	16	90–111	87–115	85–118	82–123	79–126
5	20	91–109	89–113	87–116	84–119	82–122
6	24	92–109	90–111	88–114	85–117	84–119

such samples would also be passed as having corroborated the frog assay, the others being held for testing with a fourth group of cats. With four groups the limiting value is $M = \pm 0.072$ at odds of 1 in 20. Since this is the critical level statistically, any combined value for four groups of cats which by Equation 1 gave an observed potency below 85 or above 118 per cent would be classified as significantly different from the standard. This procedure would be valid, of course, only if the observed s_M for any given assay, as computed by Equation 2 or 2a, agrees with its expected values

within the limits of sampling error shown in the last column of Table V. These limits have been determined from the constants in Table VI of reference (2) and the s_M of any assay for which the log-dosages seem erratic should be checked before using the limiting values of M given in the table.

SUMMARY.

In the assay of digitalis extract by the cat method secular variations in susceptibility are usually disregarded, as if they were negligible in comparison with other sources of error. The variation within assays relative to that between assays has been isolated by covariance in data on the individual lethal dose of standard "Digiglusin" for 52 groups each of four cats tested simultaneously. By using the dose per cat as the dependent variate and the weight of the cat as a concomitant measure, both in logarithms, arbitrary corrections for body size which might impair the validity of the comparison were avoided. In the present case, however, the size factor did not differ significantly from unity, so that the logarithm of the conventional dosage ratio in cc. per Kg. gave substantially the same results. In either case the variation within assays was very significantly less than that between assays, the net standard deviation of the latter being 60 per cent as large as that of the former. The variation between group means was independent of the date of the test and apparently random, showing that the absence of a seasonal trend does not rule out secular variation.

When the individual values were corrected for secular variation, the distribution of the individual log-doses followed the normal curve of error and could be plotted in a form equivalent to the dosage-mortality curve of which it is a variant. Because of this relation, the mean log-dose provides the best estimate of log $-$ LD50 and its antilogarithm, the median lethal dose, is recommended in place of the usual arithmetic mean.

A modified procedure of bioassay is proposed so that the variation between groups will not bias estimates of the log-ratio of potencies or its error either in the conduct of the experiment or in the calculation of the result. The computation is illustrated by numerical examples and tables are given to show the expected precision of the method.

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SOME ECONOMIC AND SOCIAL IMPLICATIONS OF FAIR TRADE LEGISLATION.*

BY LEAVITT C. PARSONS[1]

Five hundred years before the year one A. D. there lived in China a philosopher and teacher named Kung-fu-tse known as Confucius, the founder of one of China's three great religions. Confucius was a much beloved and practical preacher whose ethical and social creed rested on his belief that there was a formula through the use of which man could make happier his contacts with his fellowmen. Confucius phrased his formula thus: "What I do not wish men to do to me, I also wish not to do to men."

Five centuries later another religious leader, preaching to a rising Occidental Civilization, offered a similar social creed. In one of the most remarkable human documents that history records, Jesus Christ closed the Sermon on the Mount with this drastic injunction: "Do unto others as you would have them do unto you."

Although one formula may be negative and the other positive, there is no conflict. Together, as supplements, they summarize my title, for do they not in fact, cover all implications of Fair Trade? Let it be known that the Fair Trade Laws serve only to record in legislation the basic principles of the Golden Rule and you have built the best defense against destructive selfish interests. However, before we can teach we must learn. For this purpose I have tried to dig out and arrange some of the facts and philosophies that I believe have an influence on how Fair Trade will work.

Without definitions we would probably be talking without direction, for the field is very large and full of obstacles that fog our vision. I define Fair Trade Legislation as that phase of the laws of social control which aims to clarify, simplify and purify business relations. With this concept in mind I will try to introduce and develop four premises.

First, Social Control, and the laws recording it, represents an inevitable social trend; *Second*, society grows constantly more complex and these advances in organization are accompanied at intervals by the appearance of new types of property, which systematically, first secure legal recognition, and then in their possession, are made responsive to Social Control; *Third*, the exercise of Social Control tends to restrict the property rights of individuals and in so doing, to a definite extent, also restricts free competition in the interests of society; *Fourth*, the exercise of Social Control tends to clarify and simplify fundamental business relations between buyers and sellers in the interest of both ethical progress and economic security.

We can set no date when laws of Social Control first operated; probably in some remote age when a local chief or king issued mandates on how his followers should behave in their relations with the state and with each other. It is sufficient to indicate that during the past one hundred years the influence of Social Control has been exerted on most businesses in most fields of activity. The gradual recognition of certain kinds of business as being "affected with the public interest," and for this reason, being placed under special restrictions in their consumer relations is the most advanced manifestation of Social Control. We call these businesses public utilities and they are legally protected from competition. A possible expansion of this group into the fields of enterprise that now enjoy free competition (through further public interference with private price structures as has been already officially inferred) represents a serious implication.

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However, the types of social control legislation with which we are immediately concerned are numerous in our daily life. You are all familiar with our city and state health and fire regulations. A new federal food and drug bill has just been passed. Child labor laws and wage control are also of daily concern. Finally, we have the various anti-monopoly laws, state and federal, which, in turn, break down into direct anti-trust laws, anti-discrimination laws and special legislation abolishing wasteful cut-price competition, principally on trade-marked merchandise in free and open competition. In most of these laws, the purpose or implications are economic. In some, including the last two, they are also of social and ethical significance.

The Fair Trade Laws with which the druggists are most immediately concerned do not relate solely to druggists' problems and should not be regarded as applying to them only. Whenever it becomes necessary in the interest of society as a whole to crystallize in legislation some trend in which the complete freedom of action of the individual must be subordinated to the best interests of society, Social Control is exerted and individual freedom from that point on is restricted. Thus, not only are the laws of social control being constantly expanded, but also they are cumulative in their effect, and such laws once voted, usually remain.

Thus, we see in Premise No. 1 that the prevention by law of such practices as "loss leaders" and hurtful price competition is a part of the same trend as has already controlled fire menace and many public health risks.

Taking up Premise No. 2, we will high-point the historical development of certain types of property. If we start back with the earliest social organizations there was but one type of private property, tangible personal property, represented largely by weapons and ornaments, utensils and women. Later, when our ancestors discovered agriculture and settled down to work land, society gradually recognized ownership in individual fields and, as wealth grew and common lands vanished, real property came into the picture. Still later, the development of agriculture and industry brought in a type of intangible personal property, representing, first, special concessions or monopolies granted by the King, and then other instruments under which the government created a monopoly property right in the product of a man's mental genius. We know this family of property to-day as franchises, letters patent and copyrights.

Somewhere in this same period of growth there developed also property rights in contracts and in this field we find bonds, insurance and even bank deposits. Finally, as the Industrial Revolution created new problems in the relationship of buyer and seller; and as consumers, in many cases, were unknown to distant producers, we find that the reputation of a conscientious manufacturer came to be reflected in the demand for his particular identified product. And, thus, first the hall-mark and later the trade-mark received a tangible value in consumer acceptance apart from and above and beyond the value enjoyed by unidentified products that were recognized as inferior. As a result, the probability that satisfied customers would seek to purchase again the same goods that they knew had yielded satisfaction, came to be recognized as the company's "good-will." In spite of the fact it was as intangible as health, it is nevertheless held as of value in the law and many cases prove the courts will guard goodwill as property protectable against injury by unfair competitors.

Probably the final step in this recognition was recorded in December 1936 when the Supreme Court in its memorable decision on the Illinois and California Fair Trade Acts definitely separated in the eyes of the trade and the law, a physical commodity from the identifying trade-mark bearing package in which it went to market. It is the protection of this new type of property that is the primary purpose of our state Fair Trade Laws, for the abuse of a trade-mark by creating a price instability not consistent with the known quality of the product, has now, when so desired by the trade-mark owner, become unfair competition, and in all but a few states, is actionable at law.

Although the school of merchandising that rests on "store goodwill" rather than "trade-mark goodwill" denies the theory of separability of goods and label and the existence of any protectable property right in the manufacturer's trade-mark as related to resale price, the implications of a "loss leader" price policy cannot be defended, either on ethical or on social grounds, and, as will be shown later, it is economically wasteful rather than constructive. For the present, it is enough to say that most of the objectors to the trend of Fair Trade Legislation are tactically in the same position as were the operators of canals when the railroads came along. Times have not changed. Self interest never will be a defense against social progress.

To sum up Premise No. 2, a new type of property, goodwill, which includes a trade-mark owner's right to set the minimum price on all items offered for sale as carrying the benefit of his goodwill, has become established both in usage and in law, and will probably continue to survive. Fair Trade Laws aim to protect both consumers and producers in the social use of this new property.

As Premise No. 3, the exercise of Social Control Legislation tends to restrict the property rights of individuals and, to a definite extent, also restricts free competition in the interest of society. There are hundreds of state laws and municipal ordinances effecting this every day. The best illustration may be the traffic laws. A motorist passively yields his rights with the clear understanding that he too benefits through the same restriction applied to others. Fair Trade Laws likewise should regulate the flow without objectionable burden, and they should supervise our operation without interfering with the way any individual chooses to run his own machine so long as he does not violate the law.

The earliest social legislation in this field of free trade restriction aimed to prevent prices from being too high. There was a wealth of such laws in the days of Queen Elizabeth. Since then, however, the Machine Age, which introduced and multiplied the middlemen, created new distributor groups, all of which are gradually finding protection in the law. It is to guard these that social legislation now takes its new direction. Gradually a legal framework is being built up which now seeks to set bottom prices, the abuse of which may some day be regarded just as illegal and just as morally wrong as are prices that are too high.

Although the most effective social legislation in this field has to do with prices, it is not price-fixing. Personally, I feel that direct price-fixing legislation is both economically futile and socially wrong. It has never been successful for any long period and can be resorted to successfully, only as a war or emergency measure when its object is frankly to check price movements by legislation or proclamation. I have had a chance to see such price-fixing attempts both here and in France. It is just as bad as it is complicated, for it aims to arbitrarily peg prices sometimes in the face of basic trends. Further, it breeds bootlegging and political corruption. However, all the early English anti-monopoly statutes had a different legal motivation. They sought to forbid any planned artificial price advance, the purpose of which was to profit at the public expense, regardless of the exact price exacted.

Under our new philosophy, free competition is being restricted by laws which now put a legal bottom under certain kinds of prices. In these laws the state for the first time has extended its protective wing to cover middlemen, and so it binds competing merchants. It has been a long fight. The Sherman Anti-Trust Act was unable to touch it. The Clayton Act two decades later did not stop it. They properly forbad horizontal agreements. Neither of these important measures recognized the fact that a vertical price contract was not necessarily in restraint of trade and that predatory competition could be just as much an instrument of monopoly as conspiracy or combinations. Yet, in spite of specific Supreme Court cases against the legality of vertical price agreements, Justice Holmes showed that the purpose of resale price maintenance was not in itself unsocial, and that the practice could be carried out within the law. It was his minority opinion in the Dr. Miles case some twenty-five years ago that started General Electric and Westinghouse selling price-protected lamps on a consignment basis and inspired the recently revived "del credere" system of agency distribution.

However, the small retailer still had no legal protection from injury if neighboring dealers used "loss leaders." Clearly, the only answer lay in new laws that aimed directly at specific types of unfair competition involving irregular or unfair pricing. The first law in this field was the Robinson-Patman Act. Although the Law itself is wordy and a bit ambiguous, its social purpose is very clear. It aimed to forbid secret discrimination in prices as between middlemen. It did not seek to reach the consumer. Its value lies in its intent rather than its technical language. It makes both buyers and sellers think about the Golden Rule. They must ask themselves, "Is this trade fair?" for under the law, they must now do unto others equally and without prejudice. To-day we realize that though this law stops discriminatory discounts and secret rebates, it does not touch retail prices or predatory competition. Originally it was otherwise represented, even by some sponsors of the bill. But the trade was well aware of what it needed and even during these debates the required protection was already being written in several scattered state legislatures.

These legal restrictions on predatory price wars first found expression in the machinery of vertical price maintenance contracts affecting intrastate commerce. Valid contracts applied only to trade-marked goods in free and open competition and were optional with the trade-mark owners. The Tydings-Miller Bill served merely to save the old conspiracy penalties of the Federal Anti-Trust Laws from falling on those who sought to carry out across state lines the execution of contracts that were legal in both the states involved.

Since both the trade-mark and the optional features of these first state Fair Trade laws restricted their application, hurtful price cutting did not cease except in certain fields. Further machinery was obviously necessary for more complete protection. To aid the unprotected, a search was made for a new line of approach.

As a result of this difference between trade-marked and unbranded merchandise, we now find two distinct groups of dealer organizations working in the field of retail price control. The original Fair Trade group is focusing on the enactment of laws permitting resale price maintenance by formal contract. This is the field the druggist pioneered. They are now supported largely by trade-mark distributors, and these groups form the backbone of the revived American Fair Trade League.

The second group under the leadership of retail food distributors and dry goods outlets, has disregarded the contract minimum price theory and is seeking to eliminate "loss leaders" by broad "floor price" legislation. They ask no standard resale price but instead a determinable cost minimum plus a standard mark up, generally around 6%, although the recently suspended Minnesota Law carried a minimum mark up of 10%.

The purpose is definitely to prevent free competition involving sales at a loss regardless of the character of the merchandise and whether or not it is packaged or identified by a trade-mark.

Although the approach and economic function of these groups differs distinctly they are not in conflict and there is nothing in the second group which restricts the operation of the first, provided the makers of a price contract do not set their minimum resale price below the cost to the dealer, which, obviously, is not likely to occur. Our main purpose here is simply to show that the major issue of outlawing "loss leaders" competition is more than the druggists' personal problem. It echoes along the entire industrial front.

However, do not let these comments give an impression that the clash between the two schools here reviewed is theoretical only. Listen to what President Paul Willis told the Associated Grocery Manufacturers, "In discussing the dealing with Fair Trade Laws and 'loss leader' laws, the first step is to understand what we're talking about. Grocery manufacturers are in favor of legislation to establish floor prices below which retailers cannot sell; they are not in favor of fixing prices or establishing high margins such as obtain in the drug industry." This paragraph from "Tide" clearly defines the issue and we who would weigh the future cannot ignore it, because it represents the sincere effort of an unprotected group to extend the protection of Social Control legislation to their particular type of business.

America is not alone in this campaign to eliminate predatory price-cutting. We must not overlook the effective way in which some foreign countries respond to this same social trend and try to protect the economic security of their small merchants by frankly restricting free competition when it employs "loss leaders" in trade-marked goods. In England, for instance, the law allows the manufacturers of proprietary products to act as a group. Here, our outmoded Sherman Act would make such action a criminal conspiracy.

Yet, in spite of our cumbersome legislative efforts, we are nevertheless conforming to the same pattern by which definite and inevitable social trends aiming to restrict abusive trade practices usually appear. As a rule, they show first on the statute books of the states, and later are consolidated in Federal legislation backed up by Federal enforcement machinery. To-day forty-three states permit resale price maintenance agreements, twenty-four have anti-discrimination laws, and ninteen prohibit sales below cost. The Robinson-Patman Act and the Tydings-Miller Enabling Act are the first steps in the national recognition of the long fought battle for permissive resale price control.

Let us now examine the fourth premise, that the increasing employment of Social Control Legislation tended to clarify and simplify the mechanics of distribution. In this I would establish but one basic change. The elimination of "loss leaders" and introduction of price maintenance

contracts, tend to restore price-making and competition by the same elementary economic process that operated prior to the Industrial Revolution. Then, prices were made by the pressure of a direct consumer demand reacting on the producers themselves.

Taking first a review of the conditions of trade in the handicraft days that preceded the factory era, we can cover this in a few statements of historic facts.

(1) The producers of goods manufactured almost exclusively for the needs of their own community; (2) There were no middlemen, and producers generally sold to consumers direct; (3) Trade organizations, we call guilds, set standards of quality and workmanship affecting the products of their members. The trade associations exercised a definite influence in Social Control; (4) Individual producers then knew individual consumers, and sales were made by a process the economist called haggling; (5) As a result of these conditions the ultimate price at which goods passed to the consumer was frankly determined solely by the producer in his appraisal of the type of consumer demand that would give him the largest volume.

With the introduction of the factory, both social and economic conditions changed and when producers began to manufacture an amount of goods above and beyond what their immediate neighborhood could consume they were faced immediately with new problems in the sound solution of which lay their destiny and economic security. Before commenting on this new direction of our more complicated process of production and distribution, we will review first some of these new problems associated with distribution to-day. (*a*) Increasing consumer consciousness; (*b*) Waste in distribution; (*c*) Price and profit determination; (*d*) Private brands *vs.* trade-marked goods; (*e*) The deal; (*f*) The trade-in.

A. Increasing Consumer Consciousness.—The striking feature here is the change in the moral attitude and legal obligations of producers toward consumers. In the earliest trading law we know it was assumed that a seller was not obliged to disclose imperfections in his goods. This early school of thought was summed up in the Latin legal phrase "Caveat Emptor," meaning "let the buyer beware." Even the clerical philosophers who wrote on business problems through the Middle Ages did not change this tradition. It was not until the Eighteenth Century that society began to feel an increasing consciousness of any obligation to protect its members from unfair trade practice. Some of the economists of the last hundred years have built up philosophic arguments on relative consumer-producer importance. One writer, Bastiat, developed a theory directly subordinating the producers to the consumers, claiming that all success in trade was solely dependent on consumer treatment. There is little doubt that many people are exploiting the new consumer protection trend for ulterior motives. Some are private research organizations and some are government agencies. However, Social Control measures, such as the Food and Drug Act, the new honest-labeling campaign of the department stores, and public statements of some of our own leaders, mean that a new day in consumer treatment is here.

B. Waste in Distribution.—To-day it costs more to sell goods than to make them. The percentage of the consumer's dollar that represents profit in distribution is very small. However the cost of marketing sometimes is more than twice the actual production cost. A recent study of the Harvard Business School shows that the operating cost of department stores has risen to over 34%. Operating cost of drug stores probably runs about 29%, while the pine board and supermarket figures range from between five and fifteen cents on each dollar of sales. One reason for this is set forth by Hector Lazo in his new book, "Who Gets Your Food Dollar." There he says that higher consumer costs are largely the result of many wholesale houses and many retail establishments attempting to give services that are not really justified. He bluntly calls these unnecessary services economic waste.

Yet, the most indisputable and obvious source of waste lies in the unfair trade practices that have crept into large scale distribution since the Industrial Revolution. These do not include poor credit and bankruptcy losses, which also, in the final analysis, must be redistributed in the pricing of future goods, and consequently they too must be paid for by the ultimate consumer.

Two or three years ago at a meeting of the American Marketing Society our guest, Mr. Lincoln Filene, was asked to discuss unfair trade practices in distribution. I still have his memoranda and I am going to review here this list of the principal causes of complaint in business transactions to-day, breaking them down into four groups.

In Group One, the retailers' complaints, we find five principal causes: (*a*) The salesman

promising things a house cannot fulfil; (*b*) Selling direct to consumer or to professional men for consumers; (*c*) Selling to competitors when line is exclusive; (*d*) Substitution of inferior merchandise in filling order; (*e*) Sending unordered merchandise.

In Group Two we find the wholesaler accuses the manufacturer on three principal grounds: (*a*) Discriminatory prices to customers; (*b*) Unsatisfactory delivery; (*c*) Selling to competitors.

In Group Three where the manufacturer complains against the wholesaler, we list three major offenses: (*a*) Unreasonable cancellation and return of goods; (*b*) Unfair pushing of competitive or private brands; (*c*) Unreasonable demand for concessions.

In Group Four, representing the complaints of the manufacturer and wholesaler against the retailer, I am inclined to add a sixth as "*f*," which since the N.R.A. is now generally recognized as "unfair:" (*a*) Failure to confirm orders; (*b*) Demanding unfair concessions; (*c*) Taking discounts not earned; (*d*) Unfair cancellations of orders; (*e*) Unjust return of merchandise; (*f*) Advertising trade-marked lines at cut prices as "bait" for substituting off brands.

If we examine critically this collection of unfair trade practices we can reclassify them as representing one or another of three different types. One group of complaints arises from just plain fraud because somebody lied. The second small group may represent merely slovenliness in business relations. And the third type might be called a profit "putsch" where one party merely tried to "jump" somebody else and grab a profit solely because he thought he could get away with it and the other fellow would not kick.

Most will admit that all these charges are unfair trade practices. The Robinson–Patman Law makes many illegal, if employed as agreed upon retailer-wholesaler relationships. Only one comes directly under consumer price-maintenance restrictions. However, I feel that all can be eliminated by a more frank application of the Golden Rule and the teachings of Confucius.

C. Price and Profit Determination.—It is impossible to seriously discuss the implications of Fair Trade without considering the part that *price* plays in our social and economic set-up. The proper determination of prices determines also the type and amount of profit. It is sufficient to say that *price* under our capitalistic system is also an effective instrument of competition. In using this instrument, the aggressive competitor is, as a rule, not concerned over the fact that the competitive price he decides to set may carry no profit to him.

As we have seen, restrictions first sought to set a ceiling against monopoly prices that might oppress the public. Now they set a floor against "loss leader" pricing, which deprives many small competitive enterprises of the possibility of profit making. To-day, we are trying to absorb this last element of Social Control. Although, in theory, Social Control should cover all similar enterprises with no more discrimination than does the weather, we still find that due to irregularities, either in the phrasing of legislation or the methods of administration, or in the courage and ingenuity of its opponents, its application is not uniform.

Gradually law and order are coming out of the price-maintenance problem and the courts are recognizing a reasonable price as protectable property. In the Calvert Case the court confirmed the referee's statement "Honest retailers of the plaintiff's goods should be protected from unfair competition of the price cutter."

Most prices in highly competitive fields are determined more by the risk of substitution than by actual cost of production. The price zones that determine the quantity production schedules in the motor car business show clearly how this theory works.

Free competition, however, does bring out noticeable price differences for the same product, which vary according to the intensity of the competition. The price reactions brought out by a study of Fair Trade Law effects, illustrate this clearly. In general these elaborate studies have proved that in the big city hot-spots the minimum prices have been raised, while in the rural and the less competitive areas the prices have been lowered. The net result has been a narrowing of the maximum variations, although the country stores will normally continue to quote higher prices for the same product than their city brothers. The reason for all this lies in an economic law that applies to all fields of merchandising. It says that retail price levels are normally set by the individual distributor's experience in competition.

One general example would be useful here as indicating what is happening everywhere. Last spring a voluminous report was released representing a careful check-up on 3203 items sold in a chain of twelve stores operating under highly competitive conditions in New York City, which showed that 2657 items or 83% of the total were unchanged in price, 9% had been lowered

and only 8% were raised. In general, as subsequent surveys also prove, prices appear to have been about half way between the makers' list price and the extreme cut prices used by the "loss leader" salesmen.

Although prices are normally determined by competition, we must not overlook the fact that profit determination or the amount of mark-up received by the distributor has some influence on price and a lot of influence on the economic security of a retail enterprise. The average mark-up determines whether a distributor shows a loss or a profit. The high frequency of a small profit may show a larger net and also greater consumer goodwill than the theory of a big mark-up when the goods don't move. However, the high frequency of sales that show no profit in themselves can never earn any net for a distributor on those items, but instead, they cost just as much money to handle as if they did show a profit.

Fair Trade Legislation has reduced the pricing problem of the druggist. He is now vulnerable to local competition rather than long distance competition through "loss leader" advertising. If he sticks to his minimum prices and pushes his volume, he should soon find himself in the happy field of growing business and unexpected profits.

D. Private Brand.—In the earliest days of trade there were no nationally advertised trade-marked brands, since the home was the factory and handicraft industries manufactured only for the needs of their own community. Producers knew their customer, and the only trademarks recognized were store brands or own brands or what in this competitive day we call a private brand.

The machine age and mass production have developed the national brand. It has been predicted that under price maintenance contracts the increased sale of private brands would steal a big share of the market formerly enjoyed by nationally advertised trade-marked lines.

If any producer of a trade-marked commodity so prices his product as to be out of line with other competing and substitutable products, he will either gain volume or lose volume in accordance with how the shopping public appraise his product price in relation to its competitors. In this purely economic process of price correction the best possible public safeguard against price abuse lies in the private brand.

On this basis the private brand enjoys a legitimate social function and under normal conditions the tendency will be that the development of private brands will help protect consumers by keeping the spread in substitutable merchandise small enough for effective price competition.

Suspicions of inferior quality in private brands are not always supported by the facts when trade-marked and private brand goods are offered on a deadly parallel basis. Whenever the clash between the two type brands represents also the clash between a reputable advocate of the "store goodwill school," and a national advertised item, then the private brand enjoys the handicap of a greater consumer acceptance, but, nevertheless, it still requires, to stimulate volume, the maximum price differential. I have frequently used examples of such a price comparison to illustrate the important function that the private brand plays in safeguarding the public against the risk of overpricing by the manufacturer of a nationally advertised trade-marked product.

A questionable feature enters the picture when, solely for the purpose of making more profit, distributors substitute long mark-up private brands for the advertised product that brought the customer into the store. We will not touch the matter of the ethics of such substitution. Sometimes it looks like fraud, at other times it merely expresses the voice of competition among the retailers on the front line of consumer service.

E. The Deal.—Although some criticize all deals whether they be Combination Deals or Free Deals as improper devices for stimulating sales, I feel, personally, that the theory of the Deal is not only a proper one, but also serves a useful economic purpose as a part of the trend toward simplifying the mechanics of competition.

Although the deal by its nature aims to capitalize the human appeal in "something for nothing," most people, including many ultimate consumers, know this is not the case. It is true that the primary appeal is a price appeal, and in a long run the profit margin in the manufacturers' prices must be sufficient to make his deals worth while. The effectiveness of any deal depends largely on the size of the jolt that can be given the retailer to jump his volume distribution.

My reason for approval, however, rests on other grounds. I see both an economical and a social justification. The first of these has to do with the fundamental rigidity of the price

structure involved in merchandising standardized packaged trade-marked goods that enjoy a national distribution. All the ingredients in any product are subject to cyclical changes in costs of materials. The cost of labor varies also. These variations cannot be reflected by changing the list prices. Hence, in periods of falling prices, manufacturers whose national policy forces them to maintain their recognized list price, still try to protect their trade against competition from lower priced private brands, by occasionally feeding to the trade attractive unit packages at abnormal but temporary market price levels. Sometimes they support their deals with competitive publicity to stimulate consumer demand. Such deals often benefit wholesalers, retailers and consumers without forcing manufacturers to juggle or even to revise Fair Trade Contracts.

My second approval involved a more fundamental fact. Since the changing process of competition is narrowing the price difference between competing and substitutable lines it is also accenting new distributor cultivation in the form of competitive deals. To me the deal represents a vehicle through which the *focus of price-making competition has passed back from the point of consumption to the sales manager's office of competing manufacturers.* In other words, the deal is merely another instrument through which we are again restoring the elementary conditions when producers competed with producers, and they themselves set the prices at which their commodities passed to the ultimate consumer.

F. The Trade-In.—Here is a great spongy morass in modern merchandising. It is pointed to as a threat to Fair Trade. However, the real threat lies not in the fact that such trades are made, but in the past indifference of some manufacturers concerned. There is, however, a secure bridge available if the manufacturers choose to draw certain types of contract. The real answer lies in practical economics, not ethics. It is a matter of how much price goes into the contract. In June of this year the General Electric led the way out with a new contract that specified the maximum allowance a dealer can grant on each new G. E. set. This ended the dealer's day of discretion. Since then other manufacturers have suggested that their distributors use the same idea. The idea is sound but not new. It is a system that long ago was found necessary in the price-protected automobile industry. Also, it is merely a little different version of your own drug-trade problem involving the use of premiums, coupons and certain types of hybrid deals. The solution lies in a clear and honest determination of a contract minimum price.

Let us now summarize the conditions of distribution to-day under the same five heads with which we viewed distribution prior to the Industrial Revolution.

1. The producers of goods now seldom manufacture for their own community alone, as mass producers they are now dependent on mass distribution.

2. Middlemen, such as wholesalers and retailers, are essential for producers to-day who seldom know personally their ultimate consumers.

3. Trade organizations are gaining both in strength and social responsibility and are again becoming factors in the exercise of Social Control.

4. The process of making prices is passing from the retailer back to the producer.

5. The final price determination will be conditioned on consumer acceptance, and the middlemen will theoretically become pipes or conduits through which the prices fixed in producer competition including deals are passed with the goods to the ultimate consumer.

The influence of Social Control will continue to be exerted and may further change the mechanics of distribution just as price-maintenance legislation and "loss leader" prohibitions have exerted their influence in the past two years.

We find four great epochs in the history of Social Control. The first and most primitive step involves the establishment of permanent government. It reflects the organization around the ruler of an administrative force, generally with no other objective than to perpetuate his power. Originally this may have been but a bodyguard, next a royal army; to-day a huge administrative bureaucracy.

The second epoch introduces a more formal relationship. Under this the ruler's subjects up to that time, completely submissive, now by collective effort exert their demands for recognition in the royal process of planning and spending. We might call this "the revolt of the taxpayers." In English history it is marked by the signing of the Magna Carta.

The third epoch was introduced when the economic liberties of a people were threatened by private monopolistic trusts and again the influence of the masses was reflected in restrictive legislation which this time aimed to clip the wings of the big corporations. The Sherman Act, state

anti-trust laws, the Interstate Commerce Commission and the creation of the Federal Trade Commission date this epoch.

The fourth period is marked by efforts to restrict the numerous abuses that had crept into the youthful system of large-scale distribution. Here is its dominant theme: Unless restrained, unscrupulous individual traders can injure society as well as their competitors.

The difference in these four epochs can be distilled into a few contrasting phrases. The first period aimed to protect the ruler against the people; the second to protect the people against the ruler; the third period aimed to protect the individual against the group; and now we are establishing, through Social Control, the protection of the group against the unscrupulous individual.

We must approach the solution of current problems with both knowledge and common sense. We must know the difference between sentiment and fact. The real difference between anarchy and an organized free society lies in the degree of individual restraint and in the kind of rules set up to insure mutual satisfaction in the economic relations of men. In a complex capitalistic economy like that in which we live such regulations usually serve as a legal framework, an invisible cage within which those who trade may freely work and play. These rules, sometimes coded, sometimes uncoded, are the formulated ritual of society as it gropes gradually toward a healthier community existence, where expanding mutual confidence brings a second reward in greater mutual satisfaction. All such rules must represent a compromise of individual freedom for community protection. They are the barometers of community morality, constantly changing to meet the altered conditions of a changing world clouded with economic storms. Thus, Social Control becomes the shining armor that protects society. Without it, there would be either chaos and confusion, or the helpless despair of economic slavery.

Another has phrased it thus: "The restraint of rules under which you work and play is the price you pay for personal opportunity, for love and content, for a home, for a certain mental and spiritual stability, for all the treasures of the past and the security of the future."

To conform to these moral and economic restraints means that you understand the basic differences between Liberty and License. To record this difference in flexible law, to guard it and to guide its growth toward a happier destiny, is the real objective of a true democracy.

There can be no real economic peace, no real moral progress until we prove by application that the philosophy of the Golden Rule is both sound and practical. Whether or not we are destined to enjoy the peace and prosperity that rightfully belong to a great people depends upon how eagerly we accept this challenge and how seriously we respond to all its obligations and restraints. Whether Fair Trade is to be remembered merely as a political catch-phase or as a living creed depends on how well you twentieth century guilds inspire your members with the two-way purposes of Social Control. In this decision, you of the A. PH. A. whose long traditions of unselfish service command respect, should rightly lead. I feel so, and I hope that in these observations you have found some fact or phrase that perhaps may serve as either sword or buckler in the great crusade for fundamental Truth and Justice that we call *Fair Trade.*

THE BACKGROUND AND OPERATION OF THE PENNSYLVANIA FAIR TRADE LAW IN THE DRUG TRADE.*

BY STEPHEN WILSON.[1]

In any study of the present situation regarding the Fair Trade Laws it is of interest to consider their legal development. While the primary interest in the Fair Trade Law is economic and commercial, the economic and legal developments are so interrelated, each having influenced the other, that a consideration of their legal development is a practical necessity. Prior to the twentieth century manufacturers had the full and unquestioned right to stipulate the resale prices of the articles they manufactured. This was clearly upheld in 1889 by the Supreme Court decision in the case of Fowle *vs.* Park, 131 U. S. 88. In this decision, the Court did not doubt that this control of resale prices by the manufacturer was in restraint of trade but held that this restraint was quite reasonable in that the merchandise was controlled by a patent and that to limit that control would be equivalent to infringement of the patent rights.

Since the beginning of the twentieth century, however, contrary to all other industrial nations of the world, the United States has departed from its former position. Manufacturers have been denied the right to exercise control over their patented, copyrighted and secretly processed goods to a large extent. The progress of this development can be divided into two stages: *first*, the denial of the right to control resale prices, which was accomplished by 1911; and *second*, the restriction of all attempts to accomplish the same purpose by various means not previously declared illegal. A third stage began with the passage of the Fair Trade Legislation of recent years.

Considering only Supreme Court decisions, the denial of the manufacturer's right to control resale prices may be briefly reviewed as follows. In 1908 in the cases Bobbs Merrill *vs.* Straus 210 U. S. 330 and Scribner *vs.* Straus 210 U. S. 352, the Court held that the sale of books at a price lower than that stipulated by the publisher did not constitute an infringement of the copyright. In this case, however, contracts were not involved as the publishers had stipulated their prices by means of notices only.

In 1911, in the case of Miles Medical Co. *vs.* Park 220 U. S. 373, the Court rendered a decision holding the stipulation of resale prices by contract to be in restraint of trade and void. While this decision held that the use of contracts was contrary to the Sherman Anti Trust Act, it applied only to secretly processed goods and not to patented articles. Since secretly processed goods and patented articles had always been considered to be analogous by the Courts, it was but a step to the next decision.

The complete downfall of price maintenance came with the decision in the case of Bauer *vs.* O'Donnell May 1913, 229 U. S. 1. In this decision the Courts held that contracts used to maintain the prices of patented goods were in restraint of trade and void. Hence the simplest and cheapest way for manufacturers to maintain resale prices on their products vanished.

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* Presented before the Section on Pharmaceutical Economics, Minneapolis meeting, 1938.

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There remained three chief ways in which manufacturers could attempt to maintain resale prices; by direct agency, by consignment selling and by refusing to sell to dealers who would not adhere to stipulated prices. The direct agency type was used to a small extent, being limited chiefly to commodities requiring considerable investment. There was no question of its legality. Consignment selling was also legal if the arrangement constituted a real consignment. In some instances, however, the Courts held apparent consignments to be merely attempts to circumvent the law. Consignment selling was limited in its use for five other reasons. It required larger capital, it required more detailed accounting and there was the vexatious problem of physical deterioration of the merchandise, as well as shifts in the demand, and changes in price. There remained only the right of refusing to sell for the convenient use of the manufacturer. This right was declared legal in the Supreme Court decision in the case of the Federal Trade Commission *vs.* Beechnut Packing Co., January 1922, 257 U. S. 441, but this decision also took away any effective means the manufacturer had of enforcing that right. The decision prohibited: (1) the use of lists of names of price cutters or of those who had sold to price cutters; (2) the employment of salesmen or agents to report or investigate instances of price cutting; (3) the reporting of the names of price cutters to wholesalers with whom the latter were not to deal; (4) the rewarding of dealers who maintained prices by turning over to them orders for merchandise solicited by the salesmen employed by the Beechnut Co.; (5) the use of serial numbers in tracing the movements of goods.

To all practical purposes this left the manufacturer with only one effective means of maintaining his prices, the buying in of all goods sold at cut prices. This was expensive and cumbersome. It meant watching the sales of every dealer, and when prices were cut it meant hiring people to go into the store as customers and buy the cut-price merchandise until the dealer had no more to sell.

Into this picture we now have the introduction of the Fair Trade Laws, first in California in 1931, and since copied by forty-one other states, making it again possible for the manufacturer to use contracts binding on all dealers in enforcing his prices. These laws have been fortified by a Federal Enabling Act and have been upheld by the Supreme Court in the case of the Old Dearborn Dist. Co. *vs.* Seagrams Distillers Corp. December 7, 1936. This decision makes such contracts binding on all dealers whether or not they are parties to the contract.

Economics of Price Maintenance.—Business is a competitive mechanism and is not based on fixed price-levels. Yet the term "price cutting" obviously infers that prices are cut or reduced below certain levels. What constitutes these levels cannot be agreed upon. Therefore, it is extremely difficult to determine just what constitutes cut prices. Nevertheless, it is necessary to consider the meaning of this term as it applies to the problem under the Fair Trade Law. Some commodities, particularly basic commodities, are priced independently of all other commodities. Costs of production are important factors in this type of pricing. Such prices may vary considerably for a variety of reasons. They may change over a period of time, in either seasonal or cyclical movements. They may change due to discrimination, the granting of special concessions, concessions to special customers, quantity discounts, allowances for advertising, trade-in allowances, and for numerous other reasons. Finally, these prices may change on a group basis, as contrasted to discrimination on a personal basis, for such reasons as geographical location, differences in costs of doing business, mistakes or different methods of computing costs of doing business. These changes revolve around a recognized standard price in each industry. The difficulty with approaching the problem from the point of view of standards is that it involves the attempt to

determine what is or should be the standard price. In addition the theory of joint costs of production and overhead or specific costs must be considered, because (1) what may apparently be a cut in price may in reality be a legitimate reduction in price resulting from the introduction of a by-product bearing part of the expenses of production, or because (2) an item which gains popular approval may be reduced in price rather than cut, because it requires less than the average overhead expense to stock and sell it since its rapid turnover is due to its popular appeal.

Some prices which are set are interdependent in nature. A store may handle thousands of items totally unrelated to each other but the prices of which are interdependent. For example, the price of a single item may be reduced even to the point of incurring a loss, in order that a larger amount of other items might be sold on which considerable profit is made. We have here a situation comparatively new in economic theory and practice. It involves a class of transactions without profit. Therefore, the price is not fixed by cost, total cost, joint cost or specific cost. The economics of this type of business consists in reducing prices on standardized well-known articles to attract customers. Its success depends upon increasing the proportion of less well-known high mark-up merchandise sold. The items reduced in price are called "loss leaders."

Loss-leader merchandising involves cumulative price cutting, constantly extending. Item after item is added to the list of loss leaders as competing merchants vie with one another to attract purchasers. The merchandise selected for use as a loss leader possesses certain definite characteristics. It must be standardized, it must be medium priced, it must have a general appeal, and this appeal must be fairly constant. These characteristics are found chiefly among those items patented and sold on a national scale.

Loss-leader merchandising lends itself chiefly to metropolitan areas of transient trade where business is not done on a personal basis. However, due to the cumulative nature of loss-leader merchandising, many neighborhood stores have been compelled to resort to it. When prices are once reduced, it is beyond the power of any individual dealer to restore them. Consequently, the manufacturer's product is cheapened and since it can no longer be sold at a profit the manufacturer loses the valuable coöperation of the dealers. As we have seen above, prior to the Fair Trade Laws, it was also practically impossible for an individual manufacturer to restore the price of his product. This resulted (1) in the loss to the public of dealer coöperation in distributing many valuable products, and (2) the subsequent promotion on the part of dealers of longer profit items which in too many instances were inferior.

Legal Basis of the Pennsylvania Fair Trade Law.—Earlier court decisions held that the retailers who had bought merchandise for resale held title to the goods and could sell them at any price they saw fit. The Fair Trade Laws, however, are based on the legal fact that, while the retailer owns the merchandise, the manufacturer owns the trade-mark. By virtue of a trade-mark or patent, a manufacturer is enabled by advertising to build up a following for his merchandise. This represents good-will. Good-will in business constitutes property in a very real sense. For this reason the manufacturer is enabled under the Fair Trade Laws to stipulate the resale prices for his merchandise in order to prevent injury to his good-will. Thus, the property rights of the manufacturer are recognized as well as the property rights of the retailer.

This legal theory has been incorporated into Fair Trade Laws in forty-two states and there are a number of sustaining court decisions. A Federal Enabling Act, without which they were seriously handicapped, has also extended the power of the state laws. This legal basis may be destroyed in two ways: *first*, by counter legislation; and *second*, by adverse court decisions Legislation repealing the Fair Trade Laws may possibly be introduced into Congress this session but there is lacking any comprehensive program. So far, the courts, classing the problem as indifferent in nature, have been content to leave the responsibility for the Fair Trade Laws on the shoulders of the legislatures and to interpret them as written.

Economic Significance of the Pennsylvania Fair Trade Law.—The Fair Trade Laws may very possibly have some far-reaching economic effects. Business in this country has been traditionally one of free competition, with prices free from artificial control and free to reflect the ebb and flow of economic conditions. There has been, however, in the past two decades, or to be more specific since the Supreme Court decision of 1889, an increasingly apparent tendency toward concentration of retail business. The small independent dealer has felt the effects of this tendency in a number of ways. He has been subjected to unprecedented price competition. He has in many instances been driven to cut prices against his will and better judgment by that scourge of

honest retailing, "the loss leader." He has suffered the loss of integrity because his fair prices have been made to look unduly high. In some lines the small retailer has either been driven out of business or has been forced to join voluntary chains in self-protection.

A number of these trends will feel the influence of the Fair Trade Laws. Some manufacturers, having promoted the laws for years, are using contracts. Some manufacturers are frankly opposed to such methods of operation. Other manufacturers don't know what to do. Considerable indecision prevails and the picture is changing rapidly. Some competent observers even feel that the entire Fair Trade movement is on the way out. In all probability, however, the underlying changes and effects of the Fair Trade Laws will not begin to operate until the present chaotic conditions have settled to something more definite.

Trade Practices after the Pennsylvania Fair Trade Law.—Immediately after passage of the Fair Trade Act many manufacturers were in a quandary. Some manufacturers welcomed the Fair Trade Acts and immediately made use of Fair Trade contracts. Other manufacturers who had come to depend almost entirely for their volume on large dealers who sold at cut prices were not in position to use Fair Trade contracts. Between these two extremes lay the large number of manufacturers who did not know what to do. However, under the Fair Trade set-up, it will be impossible to straddle the issue. The manufacturer must choose either to operate under Fair Trade contracts or to operate without them.

Under the Fair Trade Laws small manufacturers will probably gain in importance because they will be able to build up a following without fear of their products being cheapened as loss leaders, and their good-will and prestige damaged. They will find themselves on more equal footing with their larger competitors. There will also, in all probability, be a stimulus toward the introduction of new products. With the decrease in the tendency toward centralization there will no doubt be less inducement toward mergers. Many of these and other effects will not become apparent until after the present shifting picture has become more stable.

Under the Fair Trade Laws the wholesalers' position should be greatly enhanced. With the elimination of the loss leader there should be a gradual return toward the traditional method of distribution, manufacturer to wholesaler to retailer. There will also in all probability be less incentive for the wholesalers to promote their own private brands.

The retailers under the Fair Trade Acts should have better and more equal opportunity. At any rate they should have the benefits of a higher integrity or, to put it the other way, with the elimination of the loss leader they will not be placed under the stigma of being inefficient business men or of charging exorbitantly high prices on some goods.

Price cutters will not be eliminated under the Fair Trade Act. They will simply be prevented from using nationally branded merchandise as loss leaders. Most of them will still sell nationally branded goods but at contract prices. The competition will probably be transferred to their own private brand merchandise.

In a sense the Fair Trade battle has really been a fight as to who owns the customer. The national brand manufacturer feels that the customer is his and that the dealer is his agent in supplying the customers' wants. The large dealer feels that the customer is his. In-so-far as his own brands are concerned and the brands of private manufacturers whom he controls, he assumes the responsibility of finding users for the products and accordingly sets his own prices.

The consumer should obtain several benefits from the Fair Trade Laws. First of all the elimination of the tendency toward centralization will assure wide distribution. The elimination of the loss leader will lessen intensive competition in terms of price and permit room for competition in quality and service. The consumer will still be protected as competition will by no means be eliminated. As a matter of fact, competition between brands should be considerably keener. The net result should be to the advantage of the discriminating buyer.

Competition will be keenest in metropolitan areas.

In all probability only the deep cut prices will be raised—those selling below a fair price. The general level of prices should not be affected.

CONCLUSION.

The following general conclusions are the result of an attempt to measure the extent of the changes in business practices brought about by the Fair Trade Law, and are based on a survey of sixty retail drug stores in Pittsburgh:

1. That reliable measures of the extent of changes in business practices in the drug field in Pennsylvania as occasioned by the Fair Trade Law are not obtainable at the present time.

2. That for the most part druggists' bookkeeping systems are inadequate for obtaining such measures.

3. That most druggists seem to expect an increase in business rather than an improvement in the character of the business already being done. This may be due to the emphasis on the importance of volume in the minds of business men. Nearly all of the druggists interviewed spoke of increasing their net profit through "increasing their business" but seemed to overlook the fact that the net profit may be increased by doing the same amount of business more efficiently. Increased volume will make up for some inefficiency, but the best combination is to have volume and have that volume handled with efficiency.

4. That there is an intimation that some underlying changes may be slowly developing momentum, such as the predictions that the introduction of new products will increase, that small manufacturers and small retailers will have more equal footing with their large competitors, that business will return to the traditional manufacturer to wholesaler to retailer method of distribution, or that the concentration of retailers into chains will be lessened. These will probably not become demonstrable until the present confused and constantly changing Fair Trade picture becomes more clearly settled.

A CHRONOLOGY OF SOME EVENTS OF PHARMACEUTICAL INTEREST IN ANCIENT CHINA AND JAPAN.*

BY K. L. KAUFMAN.[1]

This paper is offered with a view to increasing the interest in things Oriental. Presentations at the meetings of the Historical Section of this ASSOCIATION and other similar bodies usually ignore the possibilities of historio-scientific research in the Orient, especially China and Japan. Many who lack the library facilities or linguistic training necessary to this sort of research nevertheless find the results fascinating reading.

Chinese and Japanese science offer some chronological difficulties, though the former is probably reliable except for the Pre-Hellenic period. The Chinese fondness for literary catalogs and dynastic histories has served to preserve much of the information now available. At the same time, however, it must be stated that much of the ancient literature has never been translated. Most of the translations to date have been made by people not particularly interested in Pharmacy or any other science.

In the material to follow, it should be remembered that the earliest characters are probably legendary. For this reason, the first three dates are only approximations. Other dates about which there seems to be some doubt have been indicated by a "*c*," or by a parenthetical question mark. It will be noted that there is no

* Presented before the Section on Historical Pharmacy, A. PH. A., Minneapolis meeting.

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uniformity of method for giving dates. This is due to the fact that what seemed to be the most certain dates in connection with any individual or period have been chosen.

It should be understood, of course, that no pretense of completeness is made for this paper. It simply recounts a few random events in a long and interesting history.

PRE-CHRISTIAN ERA.

?–2838. Reign of the legendary emperor Fu Hsi (also called Tien Huang Shih). He is considered the inventor of the "pa kua," or "Eight Trigrams." For this reason, he is regarded as the chief god of medicine, since Chinese physicians influence the minds and maladies of their patients by the mystical power of the "pa kua." Fu Hsi and his four successors were supposed to have reigned an average of 85 years each.

2838–2698. Reign of the legendary emperor and "Divine Husbandman," Shen-nung. He is the supposed author of the "Pen-tsao," which contained 365 drugs for various diseases and ailments. For this reason he is also considered a god of medicine.

2698–2598. Reign of the legendary Yellow Emperor Huang Ti. The "Huang Ti Nei-ching Suwen," or "The Simple Questions of Huang Ti," is traditionally ascribed to him. This work is written in the form of a dialogue between the supposed author and the court scientist. It gives the oldest Chinese views on physiology and pathology. In its present form, the book is probably not older than the fourth century B.C. This work contains a sentence which points to the circulation of the blood: "All the blood is under the jurisdiction of the heart."

c. 1800. Time of I Yin, who is supposed to have originated medical decoctions.

604–c. 510. Life of Lao Tzu, supposed author of the "Tao te ching," the "Canon or Classic on Reason and Virtue," and the founder of Taoism. This philosophy is of interest because it is the fountain-head of Chinese mysticism. The Taoists were deeply interested in alchemy. In the past, many of them spent their best years searching for the elixir of life and the pills of immortality.

450–400 (?). Time of Pien Chiao (nickname of Chin Yueh Jen), semi-mythical Chinese physician. He is credited with the authorship of one of the earliest and most popular Chinese medical works. It is called the "Nan ching," and contains 81 chapters. Some authors have credited him with the Chinese theory of the pulse. One writer says he invented the narcotic wine, here ascribed to Hua To (q. v.). The same authority therefore calls him the "Father of Narcosis."

221–210. Reign of Shih Huang-ti in China. He sent expeditions to the island of Peng-lai in the Eastern seas in order to obtain the herb of immortality. In this latter effort, he was influenced by Lu Sheng, an alchemist.

216. Birth of Shun Yu-i, Chinese physician. His medical disciples compiled many of his writings, but the original is now lost.

213. Date of the famous "Burning of the Books" episode. This was carried out by order of Shih Huang-ti, but it should be noted that books on medicine were among those exempted.

189. Death of Chang Liang, Chinese alchemist. His efforts to find the elixir of immortality led him to employ fasting, hygienic living and spiritual exercises, as well as various drugs.

c. 150 (?). Time of An Chi-sheng, Chinese druggist, who is said to have succeeded in compounding the pills of immortality. Unfortunately, however, he ascended into heaven from a mountain top and took the secret with him.

c. 145–c. 86. Life of Ssuma Chien, Chinese historian. His famous "Historical Memoirs," written about 122 B. C., records the story of a man who persuaded the emperor that gold could be made of cinnabar.

140–85. Life of emperor Wu (Han dynasty), the patron of alchemy. His friend and adviser was probably Li Shao-chun. The latter was an apprentice of An Chi-sheng.

Alchemy is said to have been introduced into China from Greece, *via* Bactria, during the second century B.C. A few authors, however, believe that alchemy originated slightly earlier in China, and was carried West by the influence of the emperor Wu.

122. Death of Huai Nan Tzu, Chinese alchemist. His "Hung Lieh Chieh" is a treatise on cosmology embodying alchemical doctrines. This is a part of the Taoist lore. It is likely that he was the prince who supposedly discovered the elixir of life (Taoist legend).

THE CHRISTIAN ERA.

The Chinese are said to have begun the practice of dyeing the hair about the beginning of this era.

7. Wang Mang orders the court physicians to study human anatomy. This does not seem to have been enforced a very long time.

22. Death of Liu Hsin, Chinese scholar and astronomer. He wrote a chronology of very scientific appearance for prehistoric China. It was worthless, but readily accepted.

92. Death of Pan Ku, author of a famous cosmogonical treatise entitled "Pai hu ting." The work contains many strange notions on physiology.

142. Writing of Wei Po-yang's "Ts'an T'ung Ch'i," earliest Chinese treatise on alchemy. It is really a discourse on the preparation of the Pill of Immortality.

c. 150–200 (?). Life of Chang Chung-ching, greatest Chinese physician of his time. His "Chin kuei" was a treatise on dietetics, which enumerated many plants. His "Shang-han-lun," on fevers, was probably more popular. It contained over 100 prescriptions.

c. 190–265. Life of Hua To, famous Chinese surgeon. He is the supposed author of the "Chung-tsang-ching," an important medical work which includes many chapters on the Pulse, Physiology and Pathology. He is said to have produced general anesthesia by means of a wine called "ma-fei-san" or "ma-yao." Its composition is unknown, although some authors believe it contained hashish.

250–300. It is believed by many scholars that an investigation of the Taoist writings of this period would shed some light on early Chinese alchemy.

c. 215–282. Life of Huang Fu, Chinese physician. He was the author of a treatise on acupuncture called "Chia-i-ching." This work, which contained 128 chapters, seems to have been the basis for all later works on the subject.

223–262. Life of Chi Kang, Taoist philosopher and alchemist. He was one of the "Seven Sages of the Bamboo Grove."

233–297. Life of Chen Shou, Chinese historian. He edited the official history of the Three Kingdoms, which work contained the first mention of tea.

265–317 (?). Life of Wang Shu-ho, Chinese physician and author of a famous book on the pulse entitled "Mo Ching."

c. 281–361. Life of Ko Hung, Chinese Taoist, alchemist and physician. He wrote two medical works, and a treatise on Taoist alchemy, dietetics and magic. He seems to have made alchemical experiments requiring cinnabar.

290–307 (?). Publication of the "Nan fang tsao mu chang," by Chi Han. This was the earliest Chinese work of a purely botanical character. It described 80 species of plants in southern China.

399–410. Time of Fa Hsien's remarkable travels. The account of his trip has much valuable information on plants, chandalas (lepers ?) and free hospitals.

414. Korean physician Kon Bu sent to Japan to cure the emperor Ingyo. He represents one of the earliest links between Chinese and Japanese civilizations.

468. Korean physician Takurai sent to Japan. He settled in Naniwa, and his descendants continued the practice of medicine.

451–536. Life of Tao Hung-ching, Chinese Taoist physician and alchemist. He was the author, or editor, of the "Ming-i-pieh-lu" (sometimes called "Pieh-lu"), which was one of the most important ancient works on materia medica. It described double the number of drugs listed in the Pen-tsao. Among his other medical writings was the "Pen-tsao ching-chu," also on materia medica.

c. 588–592. Scales and tiles are imported into Japan from China.

554. The physician Oyu-Ryoda, and the pharmacists Han-Ryoho and Tei-Yuda go to Japan from Korea, taking various native drugs with them. This marked the real beginning of a period of Korean influence on Japanese medicine.

562. Probable date of the importation of the first Chinese medical books into Japan. It is said there were 29 works in the group, including those of Chang Chung-ching (q. v.).

597–649. Life of Tai Tsung (or Li Shih-min), second Tang emperor and real founder of the dynasty. He patronized art and learning. His library at Si-an-fu contained 200,000 volumes.

c. 607. Chao Yuan-fang composes a treatise which describes many diseases. It consisted of 50 parts and dealt with such varied subjects as scabies, female complaints and teeth.

c. 608. Korean bonze Kwanroku goes to Japan to further the advance of medicine there. Soon after some Japanese students were sent to China to obtain more medical knowledge.

c. 627. It is said that the use of thyroid gland for goiter is recorded in the Chinese medical literature under this date. However, no attention seems to have been paid to the discovery.

c. 650. The Tang emperor, Kao Tsung, orders a revision of the Pen-tsao, which work was directed by Li-chi (or Ying Kung). A little later, a new revision was edited by Su Kung (or Su-ching). The subject matter of the latter work was arranged under the headings: minerals, man, quadrupeds, birds, insects, fishes, cereals, vegetables, fruits, trees, herbs and natural objects used in medicine.

682. Death of Sun Ssu-mo, author of many Taoist medical works. Probably the most important are the "Chien-chin-fang," and the "Yin-hai-ching-wei." The former is an immense collection of recipes, including a description of the "Ulcers of Jealousy," which some authors believe may have referred to soft chancre. The latter book is a treatise on eye diseases.

685–762. Life of Ming Huang (or Li Lung-chi), sixth emperor of the Tang dynasty. He founded the Imperial Academy, which was given charge of the scientific undertakings of the empire.

724–748. Reign of the Japanese emperor Shomu-tenno, during which time the first public drug store was established in Japan.

752. Publication of Wang Tao's medical work entitled "Important Secrets of the Outer Terrace." It was very elaborate, even including a brief summary of the veterinary art.

758. Founding at Nara of the earliest Japanese hospital of any importance.

761. Publication of Wang Ping's commentary on Huang Ti's "Simple Questions." This was the earliest of the many critiques on that book.

775–800 (?). Period of greatest activity of Wake Hiroyo, Japanese physician and educator. His "Yakkei-taiso," in two volumes, was an important work on materia medica. It was based on the Pen-tsao of Su-ching. This new volume, however, contained only 254 drugs.

785–860. Life of Hiroizumi Monobe, Japanese physician and author of the earliest Japanese treatise on hygiene, the "Setsuyo-yoketsu." It is said to have consisted of 20 volumes.

812. Death of Tu Yu, Chinese writer. His encyclopœdic work on these subjects devotes one section to "food and goods."

c. 834–848. Publication of the "Chi-so-ki," by Fukuyoshi Omura. It is the earliest Japanese treatise on surgery, but is purely Chinese in its derivation.

c. 982. Compilation of the "Ishinho," by Yasuyori Tamba. This is the oldest Japanese medical work now extant in its original form. It is derived from several Chinese works. Some authors ascribe another work on materia medica to Yasuyori.

c. 1000–1050. Time of Tou Ping, Chinese chemist. He is noted for his "Chiu Pu," a work on spiritous liquors which is said to describe distillation.

1027. Wang Wei-te makes two copper figures of the body to illustrate the art of acupuncture. Three hundred sixty-seven places were indicated. He also wrote on this subject.

It is said that prophylactic inoculation was practiced in China as early as the eleventh century. The method probably originated in India.

1030–1093. Life of Shen Kua, Chinese author, mathematician, astronomer and instrument maker. He wrote the "Su-shen liang-fang," a work on medicine.

c. 1090. Publication of Pang An-shih's work on fevers. His pupil, Tung Ping, added a glossary and an appendix to this book.

c. 1093. Publication of Chien-i's book on children's diseases.

Other Chinese writers of this period described various plants and animals. Some of these works might be of interest to the pharmaceutical historian.

The bibliography which follows lists the quite common sources of material used, all of which might be found in any college library.

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PASTES. I. FOR DERMATOLOGIC USE.*

PRELIMINARY REPORT.

BY BERNARD FANTUS,[1] M.D. AND H. A. DYNIEWICZ,[1] PH.C.

We propose that the term "paste" be defined as a "water-soluble gel for medical use." This definition is intended to include semi-solid preparations of various degrees of consistency as required by their respective uses. If this definition of "paste" be accepted, then the title of Paste of Zinc Oxide and other "pastes" of fatty nature would have to be changed. Even if we had no other class of preparations for which this term is so much more appropriate as to make this change of meaning mandatory, the change would be desirable as there is no justification from the standpoint of etymology or even common use of the word for applying it to salves. The word is derived from the Greek meaning "barley porridge," possibly originally a salted mess of food. It is defined in the Century Dictionary as a compound in which a sufficient amount of moisture is present to "make a mass without liquefying." We, therefore, advocate that the present official use of the term "pastes" be abolished and that some other term such as "dense ointment" be substituted for those preparations to which the former term is at present applied. Thus, *e. g.*, the official title of *Pasta Zinci Oxidi* might be changed to "*Unguentum Zinci Oxidi Densior*" and that of the *Pasta Zinci Oxidi Mollis* be changed to "*Unguentum Zinci Oxidi Mollis*."

We believe that the clinical value of pastes in the sense in which we shall use the term here has not been adequately appreciated and for this reason we have devoted the last several years to a study of their pharmaceutic and clinical possibilities.

Owing to the importance of being able to specify a definite consistency for pastes, which needs to vary in accordance with different uses, we have spent a good deal of time in attempting to secure a simple method of standardizing paste

* Presented before the Scientific Section, A. PH. A., Atlanta meeting, 1929.

[1] From the Laboratory of Pharmacology and Therapeutics, Univ. of Illinois, College of Medicine, and assisted by a grant from the AMERICAN PHARMACEUTICAL ASSOCIATION.

consistency and believe we have succeeded in developing such a method, available to every pharmacist, and have published it in a recent issue of the JOUR. A. PH. A. (1).

Powdered tragacanth is used in all the tragacanth pastes to facilitate small quantity manufacturing because they may be made within an hour. Less ribbon tragacanth, of course, is required but it takes five to seven days to swell. The ribbon form must therefore be used in lower percentage to secure the desired degree of viscosity.

Since different lots of tragacanth may produce jellies with different degrees of viscosity ("flow time"), it is necessary before preparing large quantities of any one of these pastes to experiment with small samples so as to determine thereby the exact proportion of colloid that needs to be used to secure the desired result. Dilution of the finished paste, should it be too viscid, is impractical as it would change the proportion of the other ingredients.

ULCER PASTES.

We find that probably the most important field of employment of pastes is in the treatment of sores and ulcers of various kinds and this chiefly because pastes keep the surface moist, and drying is a great impediment to healing.

An ulcer, which is defined as a surface of the body devoid of its natural covering when located upon the external surface of the body, suffers from a number of impediments to healing, chief among which is the drying effect of the atmosphere as "all cells live in water and in running water and a dried cell is a dead cell." An ulcer exposed to drying influence must sacrifice its surface layer to death in order to be able to permit healing to go on underneath the moisture-proof coating.

Providing their composition is correct, pastes may also furnish pabulum or culture medium for the proliferation of cells. Indeed, the nutritive treatment of ulcers, *i. e.*, the furnishing of suitable culture medium for cells is as yet a practically unexplored field, the first steps into which even remain yet to be taken. It is, of course, known that drying is a bitter enemy of life. By keeping the cells in a liquid medium we not only favor cell proliferation but also cell migration which it is now believed is of considerable importance in expediting the epithelization of healing skin surfaces (2). It makes, no doubt, a great difference as to what this fluid contains, and a study of the culture media that have been found suitable for the proliferation of surviving connective tissue *in vitro* will repay abundantly when applied to healing of ulcers. We have employed, on general principles, Ringer's solution; as next to water the salts contained in Ringer's solution are probably important ingredients to make a medium suitable for the survival and multiplication of cells.

We must admit, of course, that culture medium suitable for human cells may also become a culture medium suitable for bacteria. Yet the addition of any considerable amount of antiseptic is likely to be inadmissible in a culture medium for human cells for the reason that any poison destructive or even inhibitive to the life of micro-organisms is likely to have the same effect upon the cells of the human body. Clinical experience has abundantly proved however that the addition of certain bacteriostatic agents, *i. e.*, certain antiseptics in such small quantity as is required to merely preserve the paste—is entirely unobjectionable, and that the addition of specific antiseptic is of value in ulcer surfaces that are infected. Whenever a specific antiseptic is available such as zinc peroxide in micro-anærophilic infection or sulfanilamide in hemolytic streptococcus infection their addition to the paste is of therapeutic advantage.

Paste permits drainage in contradistinction to fatty dressings, so that the paste is not contra-indicated in infected ulcers, while fatty dressings are.

We have secured at the Cook County Hospital, largely under the leadership of Miss Mary L. Weston (3), nothing less than phenomenal results from the paste treatment of bed sores. We desire here to publish preliminarily a list of formulas that have been found of value for the healing of bed sores as well as of other ulcers some of which had obstinately refused to heal.

METHOD OF USING THE PASTES IN THE TREATMENT OF BED SORES AND ULCERS.

In all cases in which this is possible the ulcer crater is completely filled with the paste, a quarter of a pound or more being employed if necessary. This is then covered with a piece of water-proof cellophane quite a bit larger than the ulcer. A frame of adhesive plaster 2″ width is then employed to fasten down the cellophane. It is, of course, very necessary that the patient should not lie upon this surface as his weight is liable to break the seal. Should this happen and the dressing still be in fairly good condition a fresh portion of paste may be slipped underneath the cellophane and an additional adhesive plaster seal applied. When the patient's skin is so sensitive as not to tolerate adhesive plaster a large quantity of the paste is applied to the ulcer and a large piece of cellophane is kept in place by a binder fitting around the body. When the paste can be properly confined by an adhesive plaster frame the dressing may not have to be changed for two or three days. In other cases it may have to be changed daily.

THE ECONOMY OF PASTE TREATMENT.

We quote from Miss Weston's article (3) a statement of the saving in time and money that in a certain section of the Cook County Hospital may be ascribed to the paste therapy, which was started in January 1936.

A COMPARISON OF COST OF SUPPLIES AND TIME USED.

	1938.			1939.	
	October.	November.	December.	January.	February.
	Before Paste Therapy.			Paste Therapy.	
Sterile Supplies	$74.00	$57.00	$60.02	$22.90	$18.01
Adhesive			2.60	2.60	2.60
Cellophane				2.25	2.25
Paste				8.00	8.00
Total	$74.00	$57.00	$62.62	$35.75	$30.86

Dakin's dressings which were previously the most popular dressing for bed sores would have required in the treatment of the 16 decubitus sores dressed each day in February, a total of 25.6 hours of nursing time daily as compared with the 3.2 hours actually consumed in the paste dressing of as many sores. This shortening of dressing time is due to two factors: (1) The entire surface is not washed. Its surroundings may be. Ulcers are self-cleansing. Scrubbing and wiping them removes the delicate growing layers and delays healing. So does the use of strong antiseptics. (2) The sores are dressed as rarely as necessary usually not oftener than every day or two.

The economy resulting from shortening the hospitalization days by the much more rapid healing of the bed sores is undoubtedly even of greater importance. It is as yet incalculable.

No. 1.

Pasta Pectini Densior,

Dense Pectin Paste.

Benzoic Acid	2.0 Gm.
Pectin, citrus No. 100 grade	150.0 Gm.
Glycerin	150.0 cc.
Ringer's solution* to make	1000.0 Gm.

* *Ringer's Solution* (Bodansky's Formula).

Calcium chloride	0.25 Gm.
Potassium chloride	0.5 Gm.
Sodium chloride	8.0 Gm.
Distilled water to make	1000.0 cc.

Dissolve the benzoic acid in the Ringer's solution. Mix the pectin and glycerin in a large dry container *very intimately* so that *all of the pectin is coated with glycerin. Then, while stirring, add the whole amount of the Ringer-benzoic acid solution* and continue stirring until homogeneous.

Viscosity: Flow time test, not less than 80° and not more then 60° in one hour.

NOTE: This paste in the present state of its composition does not keep for more than a few months without liquefying.

No. 2.

Pasta Pectini Tenuor.

Thin Pectin Paste.

Benzoic acid	2.0 Gm.
Pectin, citrus No. 100 grade	60.0 Gm.
Glycerin	60.0 cc.
Ringer's solution to make	1000.0 Gm.

Dissolve the benzoic acid in the Ringer's solution. Mix the pectin and glycerin in a large dry container *very intimately* so that *all of the pectin is coated with glycerin. Then, while stirring, add the whole amount of Ringer-benzoic acid solution* and continue stirring until homogeneous.

Viscosity: Flow time test, not less than 15 seconds and not more than 20 seconds.

NOTE: This paste in the present state of composition does not keep for more than a few months without further liquefying.

The formulas for these two pastes are required because the "dense paste" is needed for the treatment of bed sores and ulcers, while the thinner paste is useful for extensively disseminated, excoriated and ulcerated skin surfaces, *e. g.*, pemphigus (4).

No. 3.

Pasta Tragacanthæ.

Tragacanth Paste.

Benzoic acid	2.0 Gm.
Glycerin	100.0 cc.
Tragacanth, powder	100.0 Gm.
Ringer's solution, to make	1000.0 Gm.

Dissolve the benzoic acid in the Ringer's solution, add the glycerin and tragacanth, allow to swell and homogenize by straining through cheese cloth and if possible a homogenizer.

Viscosity: Flow time test, not less than 20° and not more then 10° in one hour.

This tragacanth paste has yielded "phenomenal" results in the treatment of bed sores. We are as yet unable to decide whether the tragacanth paste has any advantage over the pectin paste or vice versa.

A tragacanth paste preserved by means of 1% sodium bisulfite has also been employed quite extensively and satisfactorily. Because of its evil odor it has been deleted from this formulary. It may be reintroduced should it present therapeutic advantages to the benzoic acid preserved paste.

No. 4.

Pasta Carbamidi.

Carbamide (Urea) Paste.

Benzoic acid	2.0 Gm.
Citric acid	10.0 Gm.
Carbamide (Urea)	20.0 Gm.
Tragacanth, powder	100.0 Gm.
Glycerin	100.0 cc.
Ringer's solution, to make	1000.0 Gm.

Dissolve the urea, the citric acid and the benzoic acid in the Ringer's solution, add the glycerin. To this solution add the tragacanth, allow to swell and homogenize by straining through cheese cloth and if possible a homogenizer.

Viscosity: Flow time test not more than 40°, nor less than 60° in one hour.

This carbamide paste has been found remarkably successful for the clearing up of ulcers encumbered by foul and necrotic material. The now well-known solvent power of carbamide (urea) upon dead tissue is exerted as well when it is applied in form of this paste as when it is used upon compresses and the paste may be superior in its efficiency to the compress. The shedding of the dead material is the indication for change to another variety of dressing. So is the appearance of bleeding.

No. 5.

Pasta Aethylis Aminobenzoatis

Ethyl Aminobenzoate Paste.

Benzoic acid	2.0 Gm.
Ethyl aminobenzoate	10.0 Gm.
Chloroform	20.0 cc.
Glycerin	100.0 cc.
Tragacanth, powder	100.0 Gm.
Ringer's solution, to make	1000.0 Gm.

Dissolve the benzoic acid in the Ringer's solution; add the glycerin. To this solution add the tragacanth, allow to swell and homogenize by straining through cheese cloth, if possible a homogenizer. Dissolve the ethyl aminobenzoate in the chloroform and add this solution slowly with constant trituration and triturate at intervals until the *chloroform has completely evaporated*.

Viscosity: Flow time test, not more than 10°, not less than 20° in one hour.

In painful ulcers this analgesic paste may be of value.

It is probably advisable to replace this paste by one of the simple pastes as soon as the ulcer is no longer painful because there is evidence that local anesthesia antagonizes the rapidity of healing.

No. 6.

Pasta Sulfanilamidi.

Sulfanilamide Paste.

Benzoic acid	2.0 Gm.
Sulfanilamide	8.0 Gm.
Glycerin	100.0 cc.
Tragacanth, powder	100.0 Gm.
Ringer's solution, to make	1000.0 Gm.

Dissolve the benzoic acid and sulfanilamide in the Ringer's solution; add the glycerin and tragacanth. Allow to swell and homogenize by straining through cheese cloth and if possible a homogenizer.

Viscosity: Flow time test, not more than 10°, not less than 20° in one hour.

In ulcers infected with streptococci this paste has been asked for, and glowing reports have been secured as to the rapidity with which healing was effected.

No. 7.

Pasta Zinci Peroxidi.

Zinc Peroxide Paste.

Zinc peroxide	10.0 Gm.
Distilled water, sufficient to make a paste.	

This paste suggested by Meleney and Johnson (5) for the treatment of ulcers due to the micro-ærophilic streptococcus should be listed here because of the remarkable results secured by it in these undermined and spreading ulcers that obstinately refuse to heal under other treatment. We have verified at Cook County Hospital the value of this paste in this condition, when the paste is applied to the very limit of the crevice of the undermined portions.

No. 8.

Pasta Tragacanthæ Cuticolor.

Cuticolor Tragacanth Paste.

Benzoic acid	0.2 Gm.
Tragacanth, powder	5.0 Gm.
Cuticolor powder*	15.0 Gm.
Ringer's solution, to make	100.0 Gm.

* Cuticolor Zinc Oxide Powder.

Red ferric oxide	3.0 Gm.
Yellow ferric oxide**	4.0 Gm.
Zinc oxide	93.0 Gm.

** Obtainable from Kraft Chemical Co., Chicago, Ill.

Dissolve the benzoic acid in the Ringer's solution. Add this solution to the tragacanth and allow to stand until completely swelled, and homogenize by straining through cheese cloth and if possible a homogenizer. To the cuticolor powder in a mortar add the tragacanth paste in portions with active trituration until a smooth paste results.

Viscosity: Flow time test, not more than 10, not less than 30 minutes.

In superficial excoriations, drying paste dressings are simpler in their application and offer a soothing variation such as may be secured by spreading this paste over the surface and permitting the paste to dry. Owing to the fact that this paste is being used upon such extensive surfaces as to endanger the patient from the possibility of intoxication by phenol absorption we have employed benzoic acid as the preservative instead of the phenol recommended in our formula by the same name under cuticolor preparations (7), the title of which shall have to be changed to *Pasta Cuticolor Phenolata* should both pastes be admitted to the formulary.

No. 9.

Tutamentum Cuticolor.*

Cuticolor Film.

Benzoic acid	0.1 Gm.
Alcohol	10.0 cc.
Cuticolor tragacanth paste	50.0 Gm.
Ringer's solution, to make	100.0 cc.

* *Tutamentum, i. e.*, that which protects.

Dissolve the benzoic acid in the alcohol. Add this to the Ringer's solution. Incorporate in Cuticolor Tragacanth Paste and homogenize if necessary.

Viscosity: Flow time test, not more than 25 seconds, not less than 15 seconds.

This preparation has been found efficient in superficial excoriation and as a protectant of the skin threatened by bed sores as well as of the delicate skin surface that results from the healing of a bed sore or other ulcer to prevent its breaking down. It is also employed when the ulcerated surface is too sensitive to permit of the spreading over it of a paste.

No. 10.

Pasta Bentoniti Cuticolor.

Cuticolor Bentonite Paste.

Benzoic acid	0.2 Gm.
Alcohol	10.0 cc.
*Bentonite (5 micron mesh)	10.0 Gm.
Cuticolor powder	15.0 Gm.
Ringer's solution, to make	100.0 Gm.

* Obtainable from Wyodak Chemical Co., Cleveland, Ohio.

Dissolve the benzoic acid in the Ringer's solution and add the bentonite; permit to stand until a jelly has formed. To the cuticolor powder contained in a mortar, add this gel and triturate until a smooth paste results. Finally add the alcohol and triturate well.

This paste differs from our formula given in the article on cuticolor preparations in that we have employed benzoic acid as a preservative instead of phenol to prevent possible phenol intoxication and for this reason the phenolated preparation will have to be so designated.

This paste is a drying agent which adheres tenaciously to the skin. It is employed as a preventive of bed sores when the skin has not yet broken down, as well as upon chapped or excoriated skin where it forms crusts underneath which healing readily occurs.

No. 11.

Tutamentum Bentoniti Cuticolor.

Cuticolor Bentonite Film.

Benzoic acid	0.2 Gm.
Cuticolor powder	5.0 Gm.
Alcohol	10.0 cc.
Bentonite (5 micron mesh)	5.0 Gm.
Ringer's solution, to make	100.0 cc.

Dissolve the benzoic acid in the Ringer's solution and add the bentonite; permit to stand until a jelly has formed. To the cuticolor powder contained in a mortar, add this gel and triturate until a smooth paste results. Finally add the alcohol and triturate well.

This bentonite preparation by reason of its characteristic drying qualities is much preferred by nurses to the other preparations as an application to skin surfaces threatened by excoriation but not as yet subject to it excepting to a minimal degree.

The publication of so many formulas may seem quite redundant to the inexperienced. Their development has been forced upon us by request of the nurses of Cook County Hospital in the treatment of the many varieties and conditions of sores and ulcers under their care. Our thanks are due most especially to Drs. Ebert, Cornbleet and Slepyan of the Dermatologic Clinic of Cook County Hospital, and Miss Mary L. Weston and Miss Rosalind Cohen, nurses at Cook County Hospital, who have done a great deal toward helping in the elaboration and evaluation of these formulas.

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ASSOCIATION BUSINESS

AD INTERIM BUSINESS OF THE COUNCIL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 1938–1939.

Office of the Secretary, 2215 Constitution Ave., Washington, D. C.

LETTER NO. 10.

July 10, 1939.

To the Members of the Council:

73. The Kilmer Prize. Motion No. 22 (Council Letter No. 8, page 455) has been carried with the following voting in the affirmative: Ch, Sw, Co, Mo, Ho, Ga, Mi, Li, La, Ke, Dm, Hi, Ck, Du, Ro, Je, Fi. The L. G. Balfour Company has been requested to proceed with the preparation of the Kilmer Prize Key.

74. Use of Text of N. F. VI. Motions Nos. 23 (Council Letter No. 8, page 455) and 26 (Council Letter No. 9, page 457) have been carried and the P. Blackiston's Son & Co. and Prentice Hall, Inc., have been advised. The following members voted in the affirmative: Ch, Sw, Co, Mo, Ho, Ga, Mi, Li, La, Ke, Dm, Hi, Ck, Du, Ro, Je, Fi.

The following communication has been received from Chairman DuMez of the Committee on Publications:

"Inasmuch as Mr. D. O. Haynes had permission to use portions of the Text of the N. F. V in the booklet entitled the Era Key to the U. S. P. and N. F., I can see no good reason why the Haynes and George Company should not be granted permission to use portions of the Text of the N. F VI in a new edition of this booklet. I, therefore, recommend that permission be granted on the same terms as heretofore."

(*Motion No. 29*) It is moved by DuMez that The Haynes and George Company be granted permission to use portions of the text of N. F. VI in a revised edition of the Era Key to the U. S. P. and N. F., with the usual fee of $5.00 and the customary acknowledgment.

75. Election of Members. Motions Nos. 24 (Council Letter No. 8, page 456) and 28 (Council Letter No. 9, page 458) have been carried and applicants numbered 567 to 634, inclusive, are declared elected. The following members voted in the affirmative: Ch, Sw, Co, Mo, Ho, Ga, Mi, Li, La, Ke, Dm, Hi, Ck, Du, Ro, Je, Fi.

76. Refunding Loan on Lot No. 7. Motion No. 25 (Council Letter No. 8, page 457) has been carried with the following members voting in the affirmative: Ch, Sw, Co, Mo, Ho, Ga, Mi, Li, La, Ke, Dm, Hi, Ck, Du, Ro, Je, Fi. The extension agreement, signed by President Lascoff and Secretary Kelly, and the new note for $36,400, signed by S. L. Hilton as attorney-in-fact of the ASSOCIATION, have been forwarded to the Maryland Trust Company.

77. Purdue University Student Branch. The undersigned students in the School of Pharmacy of Purdue University whose applications for membership are attached, desire to establish a Student Branch in the School and hereby request the Council to approve the formation of the Branch and the Constitution and By-Laws submitted herewith:

The following officers for the Branch were elected: *President*, George E. Osborne; *Vice-President*, Richard E. Gerding; *Treasurer*, Henry Bikin; and *Secretary*, Harry W. Schaefer.

CONSTITUTION.

ARTICLE I—*Name.* This organization shall be known as "The Purdue University School of Pharmacy Student Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION."

ARTICLE II—*Purpose.* It shall be the purpose of this organization to uphold the aims, and to aid in the pursuance of the program set forth by the AMERICAN PHARMACEUTICAL ASSOCIATION. Further, it shall undertake a feasible scheme of activity, calculated to promote scientific investigation, professional interest and an esprit de corps among students of pharmacy with whom it may have contact.

ARTICLE III—*Membership.* Section 1. The members of this Branch shall be elected from among the bona fide students of the Purdue University School of Pharmacy and students registered in the Graduate School of Purdue University who are majoring in Pharmacy, Pharmaceutical Chemistry, or Materia Medica who have met the requirements for associate membership in the AMERICAN PHARMACEUTICAL ASSOCIATION. Section 2. Two members may submit the name of

a candidate to the chairman of the Membership Committee, who will present the name of said candidate at the next meeting of the branch. In the absence of the candidate a vote shall be taken by secret ballot. A three-fourths vote of those present shall elect a candidate to membership in the branch.

ARTICLE IV—*Officers*. Section 1. The officers of the Branch shall be: (*a*) a president, (*b*) a vice-president, (*c*) a secretary, (*d*) a treasurer.

Section 2. Election of officers shall take place annually at the regular meeting in May. A majority vote taken by secret ballot shall be necessary to elect an officer, after nominations from the floor. These officers shall be installed at the same meeting.

Section 3. The duties of the officers shall be described in the by-laws of the Branch.

ARTICLE V—*Committees*. Section 1. The following committees shall be permanent standing committees of the Branch. They shall be appointed by the president at the first meeting in the academic year unless otherwise selected as provided herein. (*a*) Executive Committee. This committee shall consist of the officers of the Branch and two members elected by the Branch. The president of the Branch shall act as chairman of this committee. (*b*) Program Committee. This committee shall consist of the vice-president as chairman and four other members. (*c*) Membership Committee. This committee shall consist of three members. (*d*) Public Relations Committee. This committee shall consist of the secretary as chairman and three other members.

ARTICLE VI—*Meetings*. Meetings shall be held at least once a month, and at any other time that may be deemed advisable by the executive committee. Every member shall receive due notification of each meeting at least one week before it is to be held.

ARTICLE VII—*Quorum*. Nine members, including at least two officers, shall constitute a quorum.

ARTICLE VIII—*Fiscal Year*. The academic year shall constitute the fiscal year.

ARTICLE IX—*Presiding Officer*. In the absence of the president the next succeeding officer shall take the chair according to the following order: vice-president, treasurer and secretary.

ARTICLE X—*Annual Dues*. The dues of this organization shall be $5.00 per annum payable to the AMERICAN PHARMACEUTICAL ASSOCIATION, Washington, D. C. Two dollars of this amount will be returned to the treasury of the local student Branch. Three dollars is retained by the parent organization for which the student shall receive the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

ARTICLE XI—*Amendments*. This constitution and by-laws or any part thereof may be amended or repealed by a two-thirds vote of the members present at two successive meetings.

BY-LAWS.

1. Duties of the Officers: (*a*) The president shall preside over all Branch meetings of the Executive Committee, and shall appoint all standing committees and such special committees as he may deem necessary. (*b*) The vice-president shall exercise the duties of the president in case of the latter's absence and shall act as the chairman of the Program Committee. (*c*) The secretary shall keep a record of all meetings. He shall prepare and forward reports of such meetings, and any other correspondence necessary, to the secretary of the AMERICAN PHARMACEUTICAL ASSOCIATION. He shall keep records of all correspondence received or entered into by the Branch. He shall notify each member of the Branch of the time and place of all meetings. He shall act as the chairman of the Public Relations Committee. (*d*) The treasurer shall keep a record of all funds of the Branch. Before the last meeting of the fiscal year he shall present to the Executive Committee a financial statement for their approval. He shall make all remittances to the secretary of the AMERICAN PHARMACEUTICAL ASSOCIATION as are necessary upon receipt of funds for dues from the members, in the manner prescribed by the rules of the AMERICAN PHARMACEUTICAL ASSOCIATION. He shall present all bills and expenditures to the executive committee. He shall issue duplicated receipts for all funds received, and obtain receipts for all funds disbursed. He shall preserve a record of all such transactions.

2. All records of the Branch shall be available for examination to any member of the Branch at any time.

3. All meetings shall be conducted according to Parliamentary Law.

4. Duties of the Standing Committees: (*a*) The Executive Committee shall transact such business as may arise and need immediate action and cannot be postponed until the subse-

quent Branch meeting. It shall approve or reject all bills and proposed expenditures submitted to it by the treasurer. Approval for expenditures exceeding fifteen dollars must be obtained by a majority vote of the members present at a Branch meeting. The Executive Committee shall audit the treasurer's report and, upon approving the report, shall present it at the last meeting of the year for the approval of the members. (*b*) The Program Committee shall arrange for all programs to be sponsored by the Branch. The chairman shall advise the secretary of all invitations to guests, and acknowledgments relative to activities of the Program Committee. (*c*) The Membership Committee shall submit the names of any candidates for membership as provided in Article III of the constitution. (*d*) The Public Relations Committee shall be responsible for the publicity of the Branch and its activities.

5. All funds of the Branch shall be held in a bank account. The president and the treasurer shall act as co-signitaries for all withdrawals from this account.

6. The Branch shall enroll all members of the faculty, who are regular members of the AMERICAN PHARMACEUTICAL ASSOCIATION, as honorary members of the Branch. They shall constitute a Faculty Advisory Board.

7. Resolutions of the AMERICAN PHARMACEUTICAL ASSOCIATION, or any of its rules or laws shall take precedence over the rules or resolutions of this Branch, when the two shall be in conflict.

(*Motion No. 30*) It is moved by Little that the application to establish the Purdue University Student Branch of the ASSOCIATION and the proposed Constitution and By-Laws be approved.

78. Applicants for Membership. The following applications, properly endorsed, accompanied with the first year's dues, and recommended by two members of the ASSOCIATION, have been received:

Nos.: 635, Charles Rabe, Jr., Steeleville, Ill.; 636, Dennis E. Murphy, 3175 Linwood Rd., Cincinnati, O.; 637, Joseph Frost, 86–52 Queens Blvd., Elmhurst, N. Y.; 638, Blanche R. Fontaine, 92 Maple St., Woonsocket, R. I.; 639, Chester C. Coon, 130 Russell St., W. Lafayette, Ind.; 640, Julia C. Cornelius, Women's Residence Halls, W. Lafayette, Ind.; 641, Charles L. Boswell, School of Pharmacy, W. Lafayette, Ind.; 642, James W. Bolton, 305 State St., W. Lafayette, Ind.; 643, Henry Bikin, 704 W. 46th St., Gary, Ind.; 644, Hugh A. Cotton, 212 Wiggins St., W. Lafayette, Ind.; 645, Fred J. Daoust, 400 Northwestern Ave., W. Lafayette, Ind.; 646, George S. Denton, 503 State St., Lafayette, Ind.; 647, John J. Easley, 130 Russell St., W. Lafayette, Ind.; 648, Sister Clara Francis Faulkner, St. Francis Convent, Lafayette, Ind.; 649, Richard F. Gerding, 306 S. Grant St., Lafayette, Ind.; 650, Ruth G. Glunt, 724 W. Oak St., Union City, Ind.; 651, Kenneth A. Groom, Jr., Star City, Ind.; 652, Roscoe J. Haas, 1230 W. Stephenson, Freeport, Ill.; 653, Don J. Henry, Jr., 455 Pine Lake Ave., La Porte, Ind.; 654, Henry W. Heubner, 121 Wiggins St., W. Lafayette, Ind.; 655, John H. Houseworth, 1007 First St., W. Lafayette, Ind.; 656, Robert J. Kantz, 2828 Main St., W. Lafayette, Ind.; 657, Sister Laurina Klein, St. Francis Convent, W. Lafayette, Ind.; 658, Herbert F. Le Pevre, 617 Waldron St., W. Lafayette, Ind.; 659, Myron W. McKinney, Winslow, Ind.; 660, George E. Osborn, Rural Route 3, Rochester, Ind.; 661, John W. Petry, 427 State St., W. Lafayette, Ind.; 662, Marjorie J. Rogers, 2604 Cason St., W. Lafayette, Ind.; 663, Stewart E. Ruch, 503 State St., W. Lafayette, Ind.; 664, Colonel N. Sarles, English, Ind.; 665, Harry W. Schaefer, School of Pharmacy, W. Lafayette, Ind.; 666, Wade A. Shonower, 122 North St., W. Lafayette, Ind.; 667, Warren T. Sullivan, Jr., 502 Market St., Vevay, Ind.; 668, Joseph B. Vaughan, Route 5, Lafayette, Ind.; 669, Sister Eileen Van Ackeren, St. Francis Convent, Lafayette, Ind.; 670, Samuel D. Weldy, Jr., 1615 Maple Ave., Noblesville, Ind.; 671, Leonard W. Yoder, 216 Waldron, W. Lafayette, Ind.; 672, Irving G. Kravets, 1939 N. Lincoln Ave., Chicago, Ill.; 673, Harry L. Novack, 1210 N. 7th St., Philadelphia, Pa.; 674, Donald R. Mathieson, Room 212, Pharmacy Bldg., Lincoln, Nebr.; 675, Edward E. Schuler, 2473 Beals Ave., Detroit, Mich.; 676, Francois X. Demers, Jr., 152 Easton St., Lawrence, Mass.; 677, Harold S. Feldman, 122 Howland St., Roxbury, Mass.; 678, Myrbel Newton, 12 Clifton Rd., Wellesley Hills, Mass.; 679, Ernest W. Grant, Mattakeesett St., Bryantville, Mass.; 680, Paul H. Hauber, Allendale, Mo.; 681, Richard H. Barry, Box 721, Brownsville, Pa.; 682, Clifford T. Pacenta, 201 Minersville St., Pottsville, Pa.; 683, Sara E. Koelker, 5535 Kamin St., Pittsburgh, Pa.; 684, Stanley Bromberg, 1108 Decatur St., Brooklyn, N. Y.; 685, Aldridge K. Hardee, Jr., University of North Carolina, Chapel Hill, N. Car.; 686, Albert B. Gumer, 1388 S. Second St., Louisville, Ky.; 687, Alexander Jaret, 229 E. 60th St., New York, N. Y.; 688, David P. Bach, 11

W. 42nd St., New York, N. Y.; 689, Joseph Bander, 3670 Third Ave., New York, N. Y. 690, Wilbur E. Johnston, 178 Angell St., Providence, R. I.; 691, F. F. Housman, 920 Audubon Pky, Louisville, Ky.; 692, Donald A. Clarke, 525 E. 68th St., New York, N. Y.; 693, Conrado F. Asenjo, 803 State St., Madison, Wis.; 694, George H. Schneller, 105–19 37th Ave., Corona, N. Y.; 695, E. M. Josey, 228 Main St., Frankfort, Ky.; 696, Adolph Henning, 421 Hillside Place, South Orange, N. J.; 697, Albert Greenbaum, 157 So. Center St., Orange, N. J.; 698, Michael Iannarone, 195 S. 6th St., Newark, N. J.; 699, Irving Baker, 149 Hamilton Ave., Passaic, N. J.; 700, Virginia B. Beshirian, 101 Warburton Ave., Hawthorne, N. J.; 701, George J. Bonanno, 230 Lorraine Ave., Upper Montclair, N. J.; 702, Peter Borromeo, 436 Harrison St., Passaic, N. J.; 703, Richard C. Bozian, 100 State St., Hackensack, N. J.; 704, Salvatore Bracchitta, 417 S. Elmer St., Westfield, N. J.; 705, Vincenzo P. Capone, 346 14th Ave., Newark, N. J.; 706, Alex Chase, 402 Chadwick Ave., Newark, N. J.; 707, Philip J. Cocco, 346 S. Jefferson St., Orange, N. J.; 708, Cohen, Charles M., 48 Second St., Somerville, N. J.; 709, Arthur C. Conklin, 44 Dawson St., Belleville, N. J.; 710, Paul F. Crutchlow, 14 Walnut St., Sussex, N. J.; 711, Isadore Davis, 728 S. 20th St., Newark, N. J.; 712, Leo Dubrow, 76 Prince St., Newark, N. J.; 713, Kenneth Farber, 447 Ave C., Bayonne, N. J.; 714, Michael R. Finelli, 258 Kearny Ave., Kearny, N. J.; 715, Simpson L. Fruchtman, 14 Whittingham Ter., Milburn, N. J.; 716, Louis Garawitz, 182 Ridgewood Ave., Newark, N. J.; 717, Henry Patrick Guarino, 65 S. Day St., Orange, N. J.; 718, Albert Hirt, 88 Maple St., Teaneck, N. J.; 719, Theodore Horoschak, 414 Knickerbocker Ave., Paterson, N. J.; 720, Bernard Hyman, 146 State St., Perth Amboy, N. J.; 721, Donald Kerr, 135 Main St., Hackettstown, N. J.; 722, Hyman Lebson, 75 Main St., Lodi, N. J.; 723, Irving Levine, 186 Leslie St., Newark, N. J.; 724, Warren F. Maher, 31 High St., Butler, N. J.; 725, Arby Mintz, 47 Mercer St., Jersey City, N. J.; 726, Daniel M. Pasquale, Jr., 111 Mead St., Newark, N. J.; 727, Sigmund Piotrowicz, 144 N. 10th Ave., Manville, N. J.; 728, Henry Poche, 586 Hawthorne Ave., Newark, N. J.; 729, Frank N. Romano, 204 5th St., Hoboken, N. J.; 730, Wesley R. Ross, 31 Holsman St., Paterson, N. J.; 731, Saul Roth, 580 New Brunswick Ave., Perth Amboy, N. J.; 732, John L. Seidel, 517 Raritan, Highland Park, N. J.; 733, Isadore Singer, 113 Brighton Ave., Perth Amboy, N. J.; 734, Michael Stopen, 441 Penn St., Perth Amboy, N. J.; 735, Alexander Weiss, 198 Stevens Ave., Jersey City, N. J.; 736, George W. Wyllie, 47 N. 13th St., Newark, N. J.; 737, Hyman Zatkowsky, 218 Loomis St., Elizabeth, N. J.

(*Motion No. 31*) Vote on applications for membership in the ASSOCIATION.

E. F. KELLY *Secretary.*

EXAMINATION OF PHARMACISTS FOR THE MEDICAL ADMINISTRATIVE CORPS, REGULAR ARMY.

The War Department is announcing an examination November 13–17, 1939, to qualify candidates for appointment as Second Lieutenant in the Medical Administrative Corps, Regular Army, to fill the five existing vacancies.

Appointments will be made from pharmacists, male citizens of the United States, between the ages of 21 and 32 years, who are graduates of recognized schools or colleges of pharmacy, that is, schools or colleges approved by the American Association of Colleges of Pharmacy, requiring four years of instruction for graduation and legally authorized to confer the degree of Bachelor of Science in Pharmacy.

Examination for appointment includes physical, a written examination in Practice of Pharmacy, Pharmaceutical Chemistry, Pharmacognosy, Pharmacology, and Bacteriology, Hygiene and Sanitation and an estimate of the candidate's adaptability for military service.

Examining boards will be convened at convenient locations throughout the continental limits of the United States for the examination of candidates authorized by the War Department to appear before them. Full information and application blanks will be furnished upon request by The Adjutant General, War Department, Washington, D. C. Applications will not be considered after October 28, 1939.

PRIZE MEMBERSHIP AWARDS FOR 1939.

LOUISVILLE COLLEGE OF PHARMACY—**Albert Ben Gumer,** Greatest Scholarship Improvement (G. L. Curry).

DUQUESNE UNIVERSITY—**Richard H. Barry,** Excellence in Chemistry (H. C. Muldoon); **Sara Elizabeth Koelker,** Excellence in Materia Medica (Elbert Voss); **Clifford Thomas Pacenta,** Excellence in Pharmacy (Ralph R. Kreuer).

UNIVERSITY OF NORTH CAROLINA—**Aldridge Kirk Hardee, Jr.,** Excellence in Pharmaceutical Subjects (Henry M. Burlage).

KANSAS CITY COLLEGE OF PHARMACY—**Paul Hutton Hauber,** Excellence in Scholarship (D. V. Whitney).

BROOKLYN COLLEGE OF PHARMACY—**Stanley Bromberg,** Excellence in Scholarship.

WAYNE UNIVERSITY—Faculty Award, **Edward E. Schular,** Excellence in Scholarship.

MASSACHUSETTS COLLEGE OF PHARMACY—**Ernest W. Grant,** Excellence in Organic Chemistry (I. P. Gammon); **Myrbel Newton,** Excellence in Pharmacy (Leon A. Thompson); **Harold S. Feldman,** Excellence in Materia Medica (Wm. H. Glover); **Bernard B. Jatul,** Excellence in Business Administration (L. C. Ellis); **Francois X. Demers, Jr.,** Excellence in Analytical Chemistry (E. V. Lynn).

UNIVERSITY OF ILLINOIS—Wm. Gray Prize **Irving G. Kravets,** Excellence in Past Year's Work.

TEMPLE UNIVERSITY—**Harry L. Novack,** Excellence in Scholarship (R. L. Swain).

UNIVERSITY OF NEBRASKA—**Donald R. Mathieson,** Second Highest Scholarship (M. E. Rasdal).

ST. LOUIS COLLEGE OF PHARMACY—**Charles Rabe, Jr.,** Excellence in Past Year's Work.

CREIGHTON UNIVERSITY—Freshman Award, **Joseph Bogard,** Greatest Improvement in Ideals (Henry Rush); Sophomore Award, **Warren Rix,** Highest General Average in Chemistry (Ted Connolly); Junior Award, **Francis Walsh,** Highest Average in Biological Sciences (Severin Water); Senior Award, **Sister Rita Claire Engle,** Highest Professional Ideals (R. L. Whaley); **Edmond Killeen,** Excellence in Sophomore Chemistry (Gustave E. Cwalina).

PERSONAL AND NEWS ITEMS.

Many seminarians will be surprised to learn that Dr. Marin S. Dunn is traveling in Australia and New Zealand this summer. Dr. Dunn was elected chairman of the Seminar but felt that he would have to forego that pleasure when the opportunity came to him to visit the botanical wonders of Australia and New Zealand. He sends his regrets at not being able to be with us this year.

Professor Earl B. Fischer, vice-chairman of the Seminar thus advances to the chairmanship. Professor Fischer will preside at the Blue Ridge meetings of the 1939 Seminar.

The Tennessee Pharmaceutical Association met for the 54th time, in Memphis, July 18th to 20th. One of the most interesting and entertaining programs ever planned was carried out. Among the speakers were: Dr. V. L. Fuqua, superintendent of the Pure Food and Drug Department of the State of Tennessee; a representative of the U. S. Department of Pure Food and Drugs on, "National Pure Food, Drug and Cosmetic Act;" L. F. Mitchell, member of the State Board of Health; Robert T. Walker, member of the State Board of Pharmacy; Dr. R. G. Leland, director of Medical Research, American Medical Association, "Socialized Medicine;" George W. Cunningham, superintendent of Federal Narcotic Bureau for Tennessee and Kentucky.

The Sixteenth Annual Meeting of the History of Science Society will be held in conjunction with the American Association for the Advancement of Science at Columbus, Ohio, December 27, 1939, to January 2, 1940. The Headquarters of the Society will be at the Chittenden Hotel.

Members wishing to appear on the program should communicate with Professor Louis C. Karpinski, Department of Mathematics, University of Michigan, Ann Arbor, Michigan.

The American Council on Pharmaceutical Education met in Atlantic City on Monday, July 24th, and continued in session for some days. This being the first regular meeting of the Council this year the week was crowded with discussions. Applications for accreditment, filed by colleges of pharmacy, were given detailed study. With a few exceptions, all the colleges of pharmacy making application have been inspected. All the inspection work was

done while the schools were in actual operation. Dr. E. F. Kelly is chairman of the Council and Dr. A. G. DuMez is secretary.

Boston druggists, in a group, visited the New York World's Fair for three days, during July. The party was sponsored by the Boston Association of Retail Druggists.

During the month of July the following visited the American Institute of Pharmacy: G. Wayne Heisler, Bourbon, Ind.; Minnie M. Meyer, Pullman, Wash.; Mr. and Mrs. Joy Chapman, Washington, D. C.; Charles R. Thompson, Washington, D. C.; Sig Derman, Chicago, Ill.; Richard Agne, Washington, D. C.; Glenn Sample, Clear Lake, S. Dak.; Alexander Holzberg, Brooklyn, N. Y.; C. E. Chambers, Mexico City, Mexico; Harry B. Raphael, Chicago, Ill.; Wm. C. Kintner, Seattle, Wash.; H. Houghton, Utica, N. Y.; Mary McInerney, Syracuse, N. Y.; C. Godlewska, Utica, N. Y.; Sally Trycinka, Washington, D. C.; Klara Zoller, Utica, N. Y.; Mr. and Mrs. Gail A. Gaston, Keyser, W. Va.; Marie A. Mannino, Westfield, N. J.; Mr. and Mrs. F. P. Kranz, Jr., Logansport, Ind.; Rosario J. Mannino, Westfield, N. J.; Roy C. Boyce, Baltimore, Md.; Chloris Shade, Joliet, Ill.; R. Rukey, Chattanooga, Tenn.; C. W. Exton, Washington, D. C.; G. B. Hutchison, Louisville, Ky.; W. R. Baxter, Louisville, Ky.; R. J. Sibassie, Nantes, France; Esther Meyer, Chicago, Ill.; Helen N. Kulwin, Chicago, Ill.; Bernard B. Brody, Chicago, Ill.

Howard Reed of Boston, Mass., was elected Grand President of Phi Delta Chi, national pharmaceutical fraternity, at its 56th annual convention, recently. The fraternity was founded in 1883.

Prof. Ralph A. Beegle, for several years head of the Department of Commercial Pharmacy of the University of Oklahoma, has severed his connection with the University and on August 1st assumed his duties as Director of Sales for the Cerophyl Laboratories of Kansas City.

Among the speakers at the Canadian Pharmaceutical Association meeting, August 6th to 9th, in Halifax, were Dr. R. W. Clark, Merck & Co., Rahway, N. J., "Building the Prescription Laboratory;" and Dr. G. A. Moulton, Peterborough, N. H., "Pharmacy Grows Up."

Mr. Aquilla Jackson of Baltimore, Md., has been appointed Deputy Food and Drug Commissioner of the Maryland State Department of Health. He succeeds Dr. Robert L. Swain, who held the position from 1922 until 1939, when he resigned to assume the editorship of *Drug Topics*. Mr. Jackson is a graduate of the School of Pharmacy, University of Maryland, a past-president of the Baltimore Retail Druggists Association and the Alumni Association of the School of Pharmacy, and served as a member of the Baltimore Retail Drug Code under N.R.A.

The new Pharmacy-Chemistry Building, University of Montana, Missoula, will be formally dedicated at the annual convention of the Montana State Pharmaceutical Association in September.

The publishing house of P. Blakiston's Son & Company, Inc., specializing in scientific and medical books, has been purchased by **Horace G. White.** This business was established by Presley Blakiston in 1843, and was continuously in the Blakiston family until the death of Kenneth M. Blakiston in 1937. The policies which have made this old established concern so successful will be carried on by Mr. White, who has been connected with the company for over twenty-eight years, under the name of The Blakiston Company.

NEW NAVAL MEDICAL CENTER.

Rear Admiral Perceval S. Rossiter, formerly surgeon general of the navy, turned the first spadeful of dirt at the ground-breaking ceremonies held for the new Naval Medical Center on the Rockville Pike at Bethesda, Md., June 29th. The $4,850,000 project includes a new naval hospital, medical school, dental school, quarters for personnel, including pharmacists, nurses and hospital corpsmen and subsidiary buildings. When completed, the new center will accommodate the navy facilities now situated in Washington. Directly across the Rockville Pike from the medical center are the new National Institute of Health and the National Cancer Institute.

OBITUARY.

HENRY C. KRUCKEBERG.

H. C. Kruckeberg, pioneer Minneapolis pharmacist, aged seventy, died July 23rd, at his home. For many years he had been prominent in drug activities and served as president and secretary of the Minneapolis Retail Duggists' Association, as president of the Northwest Pharmaceutical Bureau, and for eleven years as president of the Minneapolis Veteran Druggists' Association. He had been a member of the AMERICAN PHARMACEUTICAL ASSOCIATION since 1919.

In May of this year Mr. Kruckeberg celebrated his fiftieth year as a pharmacist, having in May 1889 purchased the property where he conducted continuously a professional pharmacy.

It was at his instigation that veteran druggists' associations were formed in St. Paul, Minn., North and South Dakota, Iowa and Montana. He was an associate member of the Chicago and New York Veteran Druggists' Associations. For a number of years he had given talks before the students of Pharmacy at the University of Minnesota, in recognition of his professional standing.

Funeral services were held on Tuesday, July 25th, with interment in Lakewood Cemetery.

CLYDE MASON SNOW.

Prof. Clyde M. Snow, of Oak Park, Ill., died August 5th at West Suburban Hospital.

Professor Snow was born March 9, 1868, at Earlville, Ill., the son of Simeon E. and Arabella E. Snow. He received his early education in Earlville and graduated from the Maryland Military and Naval Academy in 1886. He graduated in Pharmacy at the University of Illinois in 1902 and received his A.M. degree there in 1910. He was instructor in Pharmacy at the latter institution from 1902–1910, and Acting Professor of Pharmacy 1910–1911; Assistant Professor 1911–1919; Associate Professor 1918–1920; Professor 1920–1936; Emeritus Professor 1936–1939; Instructor in Materia Medica and Pharmacology, College of Medicine 1918–1926; Lecturer, Chicago College of Medicine and Surgery, 1910–1911; member of the Committee on National Formulary, 1911–1930; Chairman, House of Delegates, AMERICAN PHARMACEUTICAL ASSOCIATION, 1913; member of the Illinois Pharmaceutical Association and Kappa Psi.

He was the author of "The Palatability of Medicines," "Essentials of Pharmacy," "Extemporaneous Tablet Making," "Development of the National Formulary," and "Percentage Solutions."

On February 22, 1911, Professor Snow married Miss Elsie Bowen, of Crown Point, Indiana, who survives him.

BOOK NOTICES AND REVIEWS.

The Chemistry of the Carbon Compounds, by VICTOR VON RICHTER, edited by PROF. RICHARD ANSCHÜTZ. Volume II, Third Edition, Published in the United States by Nordemann Publishing Co., Inc., 215 Fourth Ave., New York City. 656 pages. Price, $15.00.

The Richter-Anschütz series on "The Chemistry of Carbon Compounds," comprises a total of four volumes. This volume, which is number two, treats on the alicyclic series and natural products. The book was translated from Volume II/1 of the twelfth edition of Richter-Anschütz' "Chemie der Kohlensloffverbindungen," which was published in German in 1935. That book was revised by the authors of the various sections and given over to the making of this book. T. W. J. Taylor, M.A., fellow and tutor of Brasenose College, Oxford, is responsible for the organization and presentation of the book.

Ring strain stability and formation, ring transition and methods of preparation of alicyclic compounds are discussed with innumerable references to literary sources. Under alicyclic compounds the following are included: monocyclic compounds excluding cyclohexane and its derivatives, cyclohexane and its derivatives, polynuclear alicyclic compounds, terpenes and resins. Under natural products are included glucosides, tannins, lichen acid, active principles of the pepper, natural coloring matters, nitrogen-free poisons, sterols, bile acids, scymnol, vitamins and hormones.

The book is by no means elementary in its scope but on the other hand it is not too advanced for common place understanding. The subjects are treated with clarity and completeness. It is recommended to those interested in advanced and up-to-the-minute information on alicyclic compounds and natural products. There are to be found many references throughout the book for those who wish to expand on the subject at hand.—EMERSON C. BEELER.

Inaugural Dissertations. Contributions to the history of Hellebore and Veratrum, an Inaugural Dissertation to the acquisition of the degree of PH.D. at the University of Basel of Ferdinand Wick of Zuzwill, Canton of St. Gallen. The author contributes the work to Prof. Dr. H. Zornig and the head of the Institute of Botany, Prof. Dr. G. Senn, and dedicates the dissertation to his parents. The general subjects deal with Hellebore and Veratrum and the special subjects to the history of the drugs; the discussion of the study is followed by biographies, and references cover ten pages. The drugs are separately treated and present a very complete study of their uses in all countries and show extensive library research relating to culture, collection, toxicology, pharmacy, pharmacology, preservation, nomenclature, etc.

Medical Jurisprudence and Toxicology, by WILLIAM D. MCNALLY, A.B., M.D., assistant professor of Medicine and lecturer in Toxicology; Rush Medical College; attending toxicologist, Presbyterian Hospital; Attending Staff St. Joseph's Hospital, Chicago. Publishers, W. B. Saunders Co., Philadelphia and London. 400 pages. Price, $3.75.

The textbook has been condensed, (largely) from McNally's Toxicology. The essential medico legal facts have been written for students of Medicine, Pharmacy and Dentistry and for practicing physicians and others called upon for determination of causes of sudden death, conditions which bring about a question of responsibility, adulteration of foods, etc.

Part I discusses medical jurisprudence of which the first chapter deals with the procedure of the courts; the Coronor, the Workmen's Compensation and Industrial Commission District and Federal Courts. The study undertakes to look into the subjects systematically and in order that the facts may be known. A chapter is given to stains and another to X-ray and radium.

Part II is devoted to Toxicology, classified in chapters for convenience of the research worker and laboratorian under headings that group the poisons according to their characteristics.

In recent years the X-ray has been used in medico-legal diagnosis and the author of this book has shown its applicability and how traps may be set by the cross-examiner. The author points out the value when used properly in the light of present-day knowledge and on the other hand, the possibility of misunderstanding and lack of understanding in the testimony.

The subjects are thoroughly considered, but briefly. The presentations indicate how dangerous the poisons may prove to be, if not eliminated, and the varying fatal doses in individuals, by methods of administration, etc.

The symptoms, the action, condition of the individuals and idiosyncrasies; the results in appearances of animals, all present interesting studies. While of special value to those engaged in the field, much information may be gained by all who have a part in any division of materia medica. It is a valuable book for the library of physicians, pharmacists, dentists, botanists and others who may be called upon to give evidence on the action of poison drugs.

Chemists (Pharmacists) Dictionary of Medical Terms. Sixth Edition. Published by the *Chemist and Druggist.* Price 8s. 10d. The publication followed that in the *Chemist and Druggist Diary,* beginning in 1907. Physiology has added some terms; the notes relating to treatment have been discontinued, but new items have increased the total.

There is some difference in the use of medicinal products in Great Britain and the United States, but this does not detract from the value and has been taken care of by the authors by inclusion of terms not largely employed in England. For use as a medical dictionary the pharmacist will find the book useful as the terms have been selected and the price is low; however, it does not replace a larger medical dictionary.

Pharmaceutcal Latin, by JACOB S. DORFMAN, Assistant Professor of Pharamcy, Columbia University College of Pharmacy. Second Edition. 146 pages. Published by Lea & Febiger, Philadelphia, Pa. Price, $2.00.

Aids to Biochemistry, E. A. COOPER and S. D. NICHOLAS. Second Edition. 312 pages. Published by Wm. Wood & Co., Baltimore, Md. Price, $1.50.

Organisch-chemische Experimentierkunst, by DR. C. WEYGAND. Published by Johann Ambrosius Barth, Salomonst. 18 B, Leipzig C. I, Germany. Price, R.M. 43.20.

THE WHITE HOUSE
WASHINGTON

September 25, 1939

My dear Dr. DuMez:

In extending hearty congratulations to the retail druggists of the country who will observe National Pharmacy Week from October twenty-second to twenty-seventh, I wish to direct the attention of the public to the essential public health function so ably performed by American pharmacists. To them falls the task of making nature's gifts available to man.

The observance of National Pharmacy Week should command attention from the public generally, for the everyday services of the American pharmacists have helped immeasurably in safeguarding the health of the nation.

Very sincerely yours,

Franklin D. Roosevelt

Dr. A. G. DuMez,
President,
American Pharmaceutical Association,
32 South Green Street,
Baltimore, Maryland.

DR. CHARLES H. ROGERS.